UNIVERSITY OF ALBERTA

SURGEON-RELATED VARIABILITY AND OUTCOME IN RECTAL CANCER

by

GEOFFREY A. PORTER ©

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled *Surgeon-Related Variability and Outcome in Rectal Cancer* submitted by *Geoffrey A. Porter* in partial fulfillment of the requirements for the degree of Master of Science in Medical Sciences - Public Health Sciences.

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Abstract

The objective of this study was to determine if subspecialty training in colorectal surgery and /or frequency of rectal cancer resections by the surgeon are independent prognostic factors for i) survival, ii) local recurrence, iii) perioperative mortality, and/or iv) postoperative morbidity in rectal cancer.

All patients undergoing potentially curative low anterior resection (LAR) or abdominoperineal resection (APR) for primary adenocarcinoma of the rectum over the period of 1983-1990 at all five of Edmonton's hospitals were reviewed. Multiple sources of data were used to create a clinical database. Outcomes included disease-specific survival, local recurrence, perioperative mortality and postoperative morbidity. Multivariate analysis was used to test all major hypotheses.

The study included 683 patients involving 52 surgeons, with greater than five-year follow-up obtained on 663 (97%) patients. There were five colorectal-trained surgeons who performed 109 (16%) of these operations. Independent of surgeon training, 323 (47%) operations were done by surgeons performing < 21 rectal cancer resections over the study period. The operative procedure was an APR in 299 (44%) patients and a LAR in 384 (56%) patients.

On multivariate analysis, local recurrence was increased in patients of non-colorectal-trained surgeons and those of surgeons performing <21 resections. Stage, use of adjuvant therapy, rectal perforation or tumour spill, and vascular/lymphatic invasion were also significant prognostic factors for local recurrence. Similarly, decreased disease-free survival was found to be independently associated with non-colorectal-trained surgeons and surgeons performing < 21 resections. Stage, grade, age, rectal perforation

or tumour spill, and vascular/lymphatic invasion were other significant prognostic factors for disease-specific survival. Across all surgeons and procedure types, perioperative mortality occurred in 14 (2%) cases. Increased Goldman Class was the only significant risk factor for perioperative mortality on multivariate analysis. Both surgeons with colorectal training and surgeons performing ≥ 21 rectal cancer resections over the study period were associated with a reduction in specific selected postoperative complications. There was no evidence of any referral bias, because all hospitals in the region were included in this study.

As outcome is improved with both colorectal surgical training and a higher frequency of rectal cancer surgery, the surgical treatment of rectal cancer patients should rely exclusively on surgeons with such training and/or experience.

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Chapter 1

Rectal Cancer: an Overview

The purpose of this study was to determine if surgeon-related variables, specifically surgical training and experience, affect outcome in rectal cancer. This chapter provides a clinical overview of rectal cancer as it pertains to this study.

1.1 Introduction

Colorectal cancer is the second most commonly arising cancer and the second most common cancer causing death in both males and females in North America.[1] Age-standardized mortality rates have decreased slightly in females and remained constant in males over the past 30 years in this region of the world. These patterns exist despite technical advances in surgery and the increased use of adjuvant therapy.[1,2]

Rectal cancer comprises 26%-43% of colorectal cancer.[3 - 5] Potentially curative treatment usually involves surgical resection, most commonly abdominoperineal resection (APR) or low anterior resection (LAR), and may include adjuvant radiotherapy, chemotherapy, or both. The overall five-year survival in Canada of all patients with rectal cancer is 47%.[2]

1.1.1 Epidemiology

Colorectal cancer is predominantly a disease of older patients with a peak incidence in the 7th decade of life. Although it can occur at any age, only 5% of cases occur in those less than 40 years of age.[3] In the U.S. and Canada, an infant has a 5%-7% likelihood of developing colorectal cancer during his or her lifetime.

Race appears to affect both incidence and mortality from colorectal cancer. Incidence appears highest in countries of the Western world with Scotland, Czechoslovakia, Denmark, and Holland having the greatest incidence, Canada and the U.S. being of intermediate incidence, and Kuwait, Poland, and African countries having the lowest incidences.[1,6] The incidence in Latin American countries varies. Although black North Americans were previously felt to have a lower incidence of colorectal cancer than white North Americans, the incidence now appears to be equal.[1,7]

With regard to religion, Jews appear to have the highest incidence with Mormons having the lowest incidence of colorectal cancer.[7] The low incidence seen in Mormons may, at least in part, be secondary to prohibition of alcohol and caffeine by their church. Although similar restrictions have existed in Jewish culture concerning alcohol, their increased risk of colorectal cancer likely has a genetic component, as the risk persists despite adjustment for social class, ethnicity, or country of birth.[7]

Vobecky et al[8] found a threefold increased risk of colorectal cancer in individuals working in factories producing synthetic fibers. They also found an increased risk in weavers, firemen, those working with asbestos, those handling chlorinated oils, and copper smelter workers. Cumulative exposure to polypropylene, organic solvents, and dyes may also be associated with increased colorectal cancer risk.[9,10]

A great deal of research has investigated the role of diet in the pathogenesis of colorectal cancer. Landmark work by Burkitt was presented in the late 1960s and early 1970s in which the supposition was made that the low incidence of colorectal cancer incidence in Africa is due to the high fiber diet of most Africans.[11] Subsequent work in animal models seemed to show a high correlation between a high intake of animal fat and protein, and the development of colorectal cancer.[12] There is also a suggestion that the protective effect of a high fiber diet may be overcome by large quantities of dietary fat.[13] Clinical studies seem to confirm high fat diet as being associated with an increased risk of colorectal cancer,[14 - 16] although two smaller studies, both of adequate statistical power, have failed to show a relationship.[17,18]

Other factors which seem to be associated with an increased risk of colorectal cancer include previous pelvic irradiation for gynecological malignancies (especially for rectal cancer), low dietary calcium, daily alcohol consumption, ulcerative colitis, and a history of ureterosigmoidostomy.[17,19 - 23] Previous cholecystectomy and reduced physical activity may be associated with an increased incidence of colorectal cancer, although this has not been firmly established.[21,24,25] There is no known association between colorectal cancer and smoking.

1.1.2 Etiology

Cancer Polyp Sequence: It has been well established that most, if not all, cases of adenocarcinoma of the colon or rectum develop from a precursor polyp although not all polyps go on to malignancy.[26,27] The risk of malignancy is largely dependent on the type and size of the polyp.

Familial Polyposis: Several familial polyposis syndromes have been identified, with the most common being familial adenomatous polyposis. Familial adenomatous polyposis is inherited in an autosomal dominant fashion with approximately 20% of cases occurring by spontaneous mutation.[28] All patients with familial adenomatous polyposis will eventually develop colorectal cancer if left untreated.[29] Gardner's Syndrome (polyposis, desmoid tumors, osteomas of the mandible, and sebaceous cysts) and Turcot's Syndrome (polyposis and medulloblastoma or glioma) are examples of familial polyposis with varying extracolonic manifestations.[30,31]

Genetics: Although initially felt to be due to common environmental factors, family history has since been shown to be an independent risk factor for the development of colorectal cancer.[32] In addition to the hereditary polyposis syndrome (see familial polyposis), an autosomal dominant condition named hereditary nonpolyposis colorectal cancer (HNPCC) has been recognized and categorized as Lynch I and II syndromes.[33]

1.2 Rectal Cancer: Clinical Considerations

1.2.1 Anatomy

The rectum is the most distal portion of the large intestine, joining the sigmoid colon to the anus and measuring 13-16 cm. in length. Embryologically, the rectum is the terminal part of the hindgut and thus is of endodermal origin. The anus, however, develops from an invagination of ectoderm. It is this difference in origin of the rectum and anus that accounts for the histological and anatomic differences between the two structures.

There are two major landmarks in the anorectal region. The dentate line, which is best seen on endoscopic exam, represents the distal border of the rectum. Above the dentate line is the true rectum, and below it is the anal canal. The anal verge, which is easily seen on physical examination, is located approximately 2 cm. below the dentate line and is the line of junction between the perianal skin and the anal canal.[34]

Lesions in the rectum are classically located in one of three levels. Lower rectal lesions are found 0-8 cm., middle rectal lesions 8-12 cm, and upper rectal lesions 12-16 cm. from the anal verge.[35] The anal verge, rather than the dentate line is used as a landmark for these levels as it is more easily identifiable. The upper rectum is invested by peritoneum anteriorly and laterally, but posteriorly remains retroperitoneal up to the rectosigmoid junction. The anterior peritoneal reflection reaches deep into the pelvis, up to 8-10 cm. above the anal verge. Below this, the entire rectum is retroperitoneal.

1.2.2 Clinical manifestations

Rectal cancer can present in several clinical fashions. The most common symptom is the passage of red blood with bowel movements.[36] This bleeding is usually slight, but persistent and may result in significant anemia. Diarrhea, change in bowel habits and vague abdominal pain are other symptoms. Rectal pain is an unusual presenting complaint, but when present often indicates significant local invasion with sacral nerve root or sciatic nerve involvement. Weight loss may also be present, often indicating metastatic disease. Bowel obstruction is present in 7%-29% of all patients with colorectal cancer, but is less common in rectal cancer.[37] When present, it is usually insidious in onset.

General physical examination is usually unremarkable in rectal cancer. Locally advanced lesions may present with a lower abdominal or pelvic mass. Metastatic disease is suspected if hepatomegaly, ascites, supraclavicular adenopathy, or an umbilical mass (Sister Mary Joseph node) is found.[35]

Rectal examination will detect most lower third and some middle third rectal carcinomas. Although only 10% of all colorectal carcinomas are detectable on rectal examination, the risks of the examination are nonexistent and thus rectal examination should be part of all complete physical examinations. When a lesion is palpated, the location (anterior, posterior, lateral) and circumferenciality can be determined. Fixation also can be assessed. Occasionally, palpation of the presacral space may reveal hard pelvic lymph nodes representing metastatic disease. Palpation anteriorly may reveal tumour in the recto-vesicular or recto-vaginal pouch (Blumer's rectal shelf).

1.2.3 Endocscopy

There are three endoscopic tools used in rectal cancer:

Rigid Sigmoidoscopy: Inserted to its full length, the distal 25 cm of the digestive tract can be visualized; however, full insertion is only possible in 50% of patients.[38] There has been much debate regarding routine annual screening with a rigid sigmoidoscope for patients greater than forty years of age.[39-42] With over ninety million such people in the United States, the annual cost would be approximately 2.75 billion dollars.[43] In a series of 2,500 consecutive rigid sigmoidoscopies in asymptomatic patients, 8 adenocarcinomas were found.[44] At the present time, routine screening sigmoidoscopy in asymptomatic patients is not widely practiced.

However, rigid sigmoidoscopy is invaluable in the assessment of rectal carcinoma.[38,44] Size, appearance, and whether the lesion is annular can be determined. The distance from the anal verge also can be ascertained. The mobility of the lesion can be assessed and biopsies can be obtained.

Flexible sigmoidoscopy: The fiberoptic flexible sigmoidoscope has had an increasing role in the past fifteen years because of its greater length and flexibility compared to its rigid counterpart.[45,46] Disadvantages of flexible sigmoidoscopy include poorer visualization of the rectal ampulla, more difficulty in removing distal polyps, and less accuracy in determination of distance from the anal verge when compared to rigid sigmoidoscopy.[47]

Colonoscopy: The primary role for colonoscopy in rectal carcinoma is to exclude any synchronous lesions. Such lesions are found in 2%-7% of patients.[48 - 50] Ideally, colonoscopy to ensure the absence of synchronous lesions should be done prior to operative treatment of the rectal cancer. Again, rigid sigmoidoscopy is superior to colonoscopy in direct examination of the rectal lesion however, colonoscopy may be used for biopsy purposes.

1.2.4 Radiology

Barium enema: As previously mentioned a search for synchronous lesions should be undertaken preoperatively in rectal cancer. There are two ways in which this is done: colonoscopy (discussed above) and barium enema combined with flexible or rigid sigmoidoscopy. Barium enema has limited visualization of the distal 20 cm of the colon and thus always should be combined with sigmoidoscopy to adequately assess this area. Although most feel that the detection rate of colonoscopy and barium enema combined with sigmoidoscopy is similar, many prefer colonoscopy provided that the rectal lesion allows passage of the colonoscope because this approach may be made the day prior to surgery and obviates the need for a second bowel preparation (required for barium enema).[47]

Ultrasound: Two types of ultrasound have a use in rectal cancer. Preoperative abdominal ultrasound for hepatic metastases may provide valuable information although it is associated with a false negative rate of 7.2%.[51] Some surgeons employ preoperative abdominal ultrasound on all patients, while others use a more selective approach based on elevated liver function tests. The second type is endorectal ultrasound. This relatively new technology has been touted as a reliable modality to achieve preoperative staging of rectal cancer. Accuracy for determination of depth of invasion is 85%-97% and for determination of lymph nodes is

85%.[52,53] The limited accuracy in determining lymph node metastases has prevented the widespread acceptance of endorectal ultrasound in preoperative staging of rectal cancer. Endorectal ultrasound was not available in Edmonton during the study period.

Computed tomography: Prior to the development of endorectal ultrasound, computed tomography scan (CT scan) was felt to be best in evaluating pelvic disease in rectal cancer.[54,55] In centres without the availability of endorectal ultrasound, CT scan remains the investigation of choice when there is a question of extensive pelvic disease preoperatively. In addition, it may also be used to determine the presence of liver metastases.

1.3 Treatment

The primary treatment of carcinoma of the rectum is surgical and involves removal of part or all of the rectum. The two most common operations are low anterior resection and abdominoperineal resection.

1.3.1 Low Anterior Resection (LAR)

This operation is performed through an abdominal incision and involves resecting the distal sigmoid and a portion of the rectum. The sigmoid colon is then anastomosed to the distal rectum by either a hand sewn technique or by intraluminal stapler. Important aspects of this operation include a minimum distal margin beyond the tumour of 2 cm [43,56] and a wide excision of the radial mesorectum.[44,57] LAR is used for upper and some middle rectal tumours.

1.3.2 Abdominoperineal Resection (APR)

In this procedure, the distal sigmoid, entire rectum, and anus are removed through combined abdominal and perineal incisions. There is no bowel anastomosis and the patient receives a permanent end sigmoid colostomy. This operation is frequently performed by two surgeons with one performing the abdominal phase and the other the perineal dissection. Abdominoperineal resection is employed for low and some middle rectal tumors.[47]

1.3.3 Other procedures

A variety of other operations, both radical and local have been used in rectal cancer to a limited extent. As these operations are seldom employed in Edmonton and not included in this study, a thorough description of them is beyond the scope of this study. The following is a list of these other procedures with references.

Coloanal anastomosis [58]
Kraske approach (presacral) [59]
Local excision [60,61]
Electrocoagulation[61,62]
Intracavitary radiotherapy [63]
Laser coagulation [64]
Cryotherapy [65]
External beam radiotherapy[66]

1.4 Adjuvant Therapy

Owing to the lack of improvement in five-year survival rates in rectal carcinoma, there has been a great deal of research investigating the potential benefits of adjuvant therapy. The two modalities used in the adjuvant setting are radiotherapy and chemotherapy.

1.4.1 Radiotherapy

Radiotherapy for rectal cancer may be given preoperatively or postoperatively. Preoperative radiotherapy doses range from 2000 to 5000 cGy and are generally given 4 to 8 weeks prior to surgery. Preoperative radiotherapy has been shown to definitively improve resectability in patients with fixed rectal carcinomas and thus this is a well-accepted indication.[67] Among 7 randomized clinical trials with varying protocols, preoperative radiotherapy was seen to reduce local recurrence in 2 trials with a trend to increasing survival in one.[68 - 74]

Postoperative radiotherapy has the advantage of knowledge of stage of disease, thus avoiding needless radiotherapy to early stage disease. However, postoperative radiotherapy can be delayed by various postoperative complications and has no effect on malignant cells which may have spread at operation. In three randomized studies of postoperative radiotherapy versus surgery alone, none have shown a survival difference and one has shown reduced local recurrence (25% versus 16%) with postoperative radiotherapy.[75 - 77] It is very difficult to compare preoperative versus postoperative radiotherapy because preoperative radiotherapy undoubtedly downstages disease and thus comparability of stages is invalid.

1.4.2 Chemotherapy

Chemotherapy as a single adjuvant modality is generally given postoperatively; 5-Flourouracil is the single-most useful agent. In contrast to the proposed benefit of decreased local recurrence with radiotherapy, chemotherapy aims to improve survival by decreasing the incidence of metastatic disease. Laurie et al. showed a survival advantage with postoperative 5-Flourouracil and Levamisole in colorectal cancer, but this was limited to Duke's C lesions.[78]

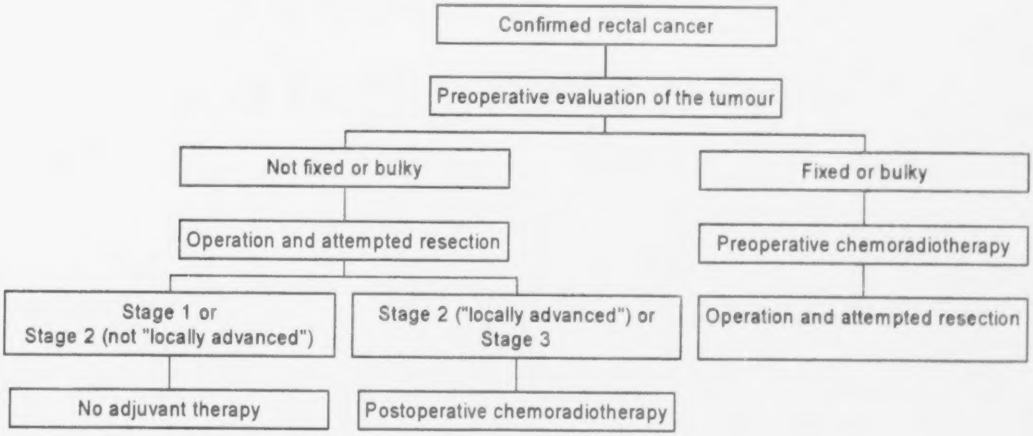
Specific to rectal cancer, there is evidence that chemotherapy both reduces local recurrence and increases five-year survival in Duke's C and "aggressive" Duke's B lesions.[79-81]

1.4.3 Combination chemoradiotherapy

With suggestion of possible benefit of chemotherapy and radiotherapy separately, combination chemoradiotherapy trials now have evolved. Unfortunately, the variety in chemotherapeutic regimes and timing of radiotherapy make these studies difficult to compare, but recent evidence with postoperative chemoradiotherapy shows a 36% reduction in cancer-related deaths over a 7-year follow up.[80] Preoperative chemotherapy with 5-Fluorouracil and Cisplatin and radiotherapy at a dose of 4500 cGy also appears to increase disease-free survival and overall survival, as well as to decrease local recurrence when compared to historical controls from the same institution not receiving any adjuvant therapy.[82]

1.4.4 Summary statement

Adjuvant therapy for rectal cancer has evolved significantly over the last twenty years. Although many indications now are well-accepted, doses and timing still are not firmly established. A reasonable algorithm for adjuvant therapy for rectal cancer is as follows:


Confirmed rectal cancer
Preoperative evaluation of the tumour
Not fixed or bulky
Fixed or bulky
Operation and attempted resection
Preoperative chemoradiotherapy
Stage 1 or Stage 2 (not "locally advanced")
Stage 2 ("locally advanced") or Stage 3
Operation and attempted resection
No adjuvant therapy
Postoperative chemoradiotherapy

The difficulty with this proposed algorithm is in definition of "fixed", "bulky", and "locally advanced", as well as in determining what comprises optimal preoperative tumour evaluation. The combination of these elusive definitions and the variation in adjuvant therapy protocols limits the comparability of these studies, a difficulty which was well recognized in the NIH consensus conference and guidelines for adjuvant therapy in colorectal cancer.[83]

1.5 Prognostic Variables

Several prognostic factors have been identified for rectal cancer. Their role and organization in this study will be further discussed in Chapter 3, Section 3.4.

1.5.1 Stage

Stage has been shown to be of prognostic significance consistently in rectal cancer in terms of both 5-year survival and local recurrence rates. Since the first reported staging system reported by Dukes in 1932,[84] many other related systems have evolved, each somewhat unique but all remarkably similar to the original Dukes' system and all shown to be of prognostic importance.[57,85-89] As can be imagined, the many staging systems and seemingly equal number of "modifications" created difficulties in comparing the literature and confusion among clinicians. The TNM system set forth in 1992[90] (Appendix 1), is the most attractive staging system at the present time for several reasons:

1. It appears to be the most widely used in the literature at the present time.

2. Even if the TNM stage is not specifically stated on a pathology report, one may be easily and accurately assigned based on the pathologic description in the report.

3. The confusion associated with the nomenclature of the various named systems (e.g., Dukes', modified Dukes', Astler-Coller, and modified Astler-Coller) is averted.

1.5.2 Grade

Grade has been shown to impact prognosis and thus always is recorded in the pathology report.[91 - 93] The classification system put forth by Blenkinsopp et al. in 1981 classifies grade into one of three categories:[94]

1. well differentiated
2. moderately differentiated
3. poorly differentiated/anaplastic

1.5.3 Size

Size of the tumour, as measured in greatest dimension, is also of prognostic significance.[95 - 97] Patients with larger or fixed tumours also may be more likely to receive preoperative adjuvant therapy. Most studies have recorded size as measured in greatest dimension, to the nearest cm., on the gross pathology specimen.

1.5.4 Level

Level of the tumour, as measured in cm. from the dentate line, often determines the operation performed. Most tumors less than 6 cm from the dentate line are treated with abdominoperineal resection while most tumors above 12 cm are treated with a low anterior resection. Many studies show increasing local recurrence and decreasing survival with more distal tumors (closer to the dentate line).[98 - 100]

1.5.5 Perforation

In addition to the aforementioned accepted clinicopathologic prognostic indicators, inadvertent perforation of the rectum has been shown to have an independent detrimental impact on local recurrence and survival in resections for rectal cancer.[101 - 103] The pathophysiology of this finding has not been elucidated. Implantation, the release of tumour cells from a primary source and secondary growth on another surface, may help to explain this finding. However, doubt has been cast on the viability of the exfoliated neoplastic colonic cell.[104] It is conceivable that, at least in part, inadvertent perforation is simply a marker for an inferior resection and thus may be further evidence towards surgeon-related factors influencing outcome.

1.5.6 Blood transfusion

Several retrospective analyses have found perioperative blood transfusion to be associated with an increased risk of tumour recurrence.[105 - 107] A recent meta-analysis[108] and prospective clinical trial[109] seem to support a poorer prognosis for patients undergoing perioperative blood transfusion. Initially, this phenomenon was presumed to have an immunologic basis.[110] However, the recent finding of equally poor prognosis with allogenic and autologous transfusions suggests that this is not the case.[111] In fact, it appears that the detrimental impact of blood transfusion is primarily from increased local recurrence, suggesting that the factors **necessitating** transfusion are of prognostic significance. This certainly has a potential implication in this study.

1.5.7 Adjuvant therapy

Please see Chapter 1, Section 1.4 for a discussion of this topic.

1.5.8 Operative procedure

Some studies have shown a difference in local recurrence and survival with anterior resection versus abdominoperineal resection.[112,113] The more recent literature suggests that there is indeed no difference[114 - 120] and that the difference seen in the previous studies is from the "coning-down" effect during low anterior resection, in which the surgeon is not completely resecting the mesorectum to the level of the tumour.[120] There also may be a tendency for some surgeons (possibly colorectal-trained or more experienced) to perform proportionately more low anterior resections than other surgeons.

1.5.9 Age and gender

Neither age nor gender have been shown definitively to be of prognostic significance for death from recurrent or metastatic cancer.[91,96,121] Chapuis et al.[86] did show a significant improved overall survival (death from all causes) in both younger and female patients. Of course, it is important to remember that both age and gender are influenced by death from other causes.

1.5.10 Other factors

Several other factors have been implicated with increased local recurrence and decreased survival in rectal cancer. These include fixation to adjacent organs [86,91,93] preoperative CEA>5ng/ml [91,93,122,123] vascular or lymphatic invasion [121,124] and presence of obstruction.[86,93,112]

1.6 Survival Analysis and its Application in Rectal Cancer

Prognosis is useful when considered as the likelihood that patients with a given condition will experience an outcome at a future time. This is not available when prognosis is presented simply as a summary rate. The easiest way to determine true survival would be to assemble a cohort of patients at a similar point in their disease (e.g., at diagnosis) and keep them under surveillance until either they all developed the outcome of interest or until the period of interest had lapsed, whereupon a survival curve could be constructed. However, this is usually impractical and inefficient as some patients may drop out of the study while others may die of other causes and thus not have the possibility of developing the outcome of interest. Moreover, outcomes (e.g., death) may not be obtained in all patients with a disease (e.g., cancer) over a defined period of time. It is for this reason that survival analysis techniques, which are in fact limited to the analysis of events such as death or recurrence, are used in medical research examining outcomes in health care.

In the life-table method of survival analysis, the chance of surviving to any point in time is equal to the cumulative probability of surviving each of the time intervals that precede it. Such intervals are predetermined and may be as small as days or as long as years. In intervals where nobody experiences the event, the probability of surviving is one or unity. For intervals where one or more patients experience the event, the probability of surviving that interval is the ratio of patients not experiencing the event of interest to the number of patients at risk of experiencing the event during the interval. Patients who are not at risk of the event, for example from loss to follow-up or death from other causes, are not used to estimate survival for that interval and are considered "censored". Although these interval estimates of survival probability are not very accurate, the overall probability of survival is remarkably precise.

The Kaplan-Meier method is similar to the life-table technique except that it requires an event occurs in all intervals, and thus not all intervals are of equal length.

Health-related research questions often involve the comparison of survival between cohorts of patients which may differ in treatment or prognosis. Survival curves for each cohort can be constructed as previously described, and their respective curves compared by several statistical tests.[125] This comparison not only examines differences in survival rates at the end of the period, but also compares the shapes, or times to event, of the survival curves. A regression technique has been developed to examine survival curves in a multivariate way.[126] The specifics of this statistical approach to this technique will be addressed in Chapter 3.

In the medical literature, there has been widespread application of survival analysis techniques over the past 10-15 years.[127] Survival analysis has become a standard descriptive and analytic tool in medical research, particularly in the cardiology and oncology literature. Specifically, by the end of 1993, Cox's landmark article[126] describing proportional hazards regression had been referenced over 7,000 times.[127,128] Moreover, studies utilizing survival analysis to specifically assess health outcomes have become more prevalent in the medical literature.[127] Reasons for this phenomenon may include a more widespread acceptance and understanding of these techniques, and easier access to computer software packages with the ability to perform such analyses.

Similarly, rectal cancer studies containing survival analysis in examining outcome are common. However, as seen in other areas, a problem has been in the specific outcome examined. "Survival" is often not defined and may refer to disease-specific, event-free or overall survival. Furthermore, most studies report only five-year rates, presumably for comparison with older studies not using survival analysis and simply reporting five-year crude survival rates.[47]

Chapter 2

Rationale and objectives of the study

This chapter provides a review of the pertinent literature relating to surgeon-related variability. The objectives and hypotheses of the study are reviewed and the relevance of this study is discussed.

2.1 Evidence for Surgeon-Related Variability Predicting Outcome in Cancer

2.1.1 Other cancers

Variation in survival for patients with various neoplasms has been shown across regions and countries of Europe.[129] Specifically, significant variation was seen for breast cancer patients. Sainsbury et al [130] retrospectively identified treatment variations among surgeons in breast cancer, but did not examine outcome, in terms of survival, of such variations. In subsequent work,[131] Sainsbury showed that patients of surgeons who had performed more than 30 breast cancer operations per year had improved survival in a multivariate model. This study also showed that the surgeons' use of adjuvant therapy accounted for part, but not all of this survival advantage.

Matthews et al.[132] retrospectively compared the outcome in esophageal carcinoma among surgeons who performed more than 5 esophageal resections per year with that of surgeons performing less than 3 resections per year over a twenty year period. A significantly increased operative mortality in the group performing fewer resections (39.4% vs. 21.6%, p=0.001) was found, however no significant difference in 5-year survival was seen after adjusting for operative mortality. A similar phenomenon was noted after pancreaticodeodenectomy for pancreatic cancer in which surgeons performing more resections had lower rates of postoperative pancreatic fistulas, a major source of morbidity.[133] Survival was not addressed in this study.

2.1.2 Rectal cancer - indirect evidence

Perhaps the strongest indirect evidence linking surgical factors and outcome in rectal cancer is the wide range of reported local recurrence rates of 2.6%-38%.[113 - 120,134] Although the inclusion criteria and use of adjuvant therapy differed somewhat among these studies, this is unlikely to completely explain the wide variation in local recurrence which is consistently reported.

Heald [134 - 136] and colleagues suggest that the large variation seen is due to a difference in what the surgeon feels to be a curative resection, specifically in reference to the radial margin, which in the rectum is the so-called mesorectum. Heald consistently has reported a low local recurrence (4% at 10 years), and argues that reducing local recurrence is at least partly accomplished by removing tumour cells in the mesorectum. He describes the "Holy Plane" beyond the mesorectum which he feels is critical to successful rectal cancer surgery. Although some patient selection issues may contribute to his results,[137] the low local recurrence rates in his patients cannot be disregarded, especially as none of his patients received adjuvant therapy. Furthermore, independent review of Heald's series supports his findings.[136]

In the past, it has been suggested that for tumours in the mid (6-12cm) or low (0-6cm) rectum, there is a higher local recurrence rate with low anterior resection than abdominoperineal resection.[112,113,138] This claim has been disputed in a number of similar uncontrolled studies.[114 - 120] Although the results of many of these studies may be questioned because of small sample size and resultant inadequate statistical power, there remains a conflict of results. A plausible explanation for this conflict would be that of surgeon-related variability; specifically in reference to the "coning-in" effect described during low anterior resection resulting in a violation of the mesorectal plane.[139]

Reinbach et al.[140] examined the type of resection performed in colorectal cancer and compared surgeons with an interest in colorectal surgery and surgeons with other subspecialty interests ("interest" was not well defined). They showed surgeons with an interest in colorectal surgery resected twice as much colon and were more likely to remove adjacent clinically involved organs for both left-sided and rectal neoplasms. This study did not examine complications or outcomes.

Hakema et al.[141] showed a wide variation in survival from colorectal cancer among 21 hospital districts in Finland after adjustment for age and stage. They also found improved 5-year survival in patients from University hospital districts when compared with patients from non-University hospital districts. However, a similar study in England showed no significant difference in operative mortality or 5-year survival in colorectal cancer patients receiving their operation, analyzed by teaching hospital or district general hospital affiliated surgeons.[142] Although rectal cancer patients were included in these studies, stratification for rectal cancer was not performed.

2.1.3 Rectal cancer- direct evidence

A German population-based study of rectal cancer showed a correlation between survival and districts with higher rectal cancer incidence to population ratios.[143] The authors thus suggest that surgical experience affects outcome. This study, however, does not present statistical significance nor is any attempt made to control for confounding factors.

McCardle and Hole[144] analyzed a cohort of colorectal cancer patients operated on by 13 surgeons between 1974-1979. None of the involved surgeons had a particular interest in colorectal surgery. They found a wide variation in both postoperative complications and 5-year survival among the surgeons involved. In a Cox proportional hazards regression model incorporating other identified prognostic factors, statistically significant hazards ratios for 5-year survival in 3 of the surgeons (0.56, 1.83, 2.03) were identified.

Phillips et al.[112] found a wide variability in local recurrence rates from colorectal cancer among 20 consultant surgeons in Great Britain. This significant variation remained after adjustment for other independent prognostic factors. This effect appeared in both colon and rectal cancer after stratification. It was unclear, however, as to the training or interest of the involved surgeons, and survival was not assessed.

In the a recent study, Hermanek et al.[145] suggested that the individual surgeon was an independent prognostic factor for locoregional recurrence in rectal cancer. This conclusion was based on the finding of significantly higher local recurrence rates among surgeons performing rectal cancer resections less frequently. However, in their analysis, they excluded a surgeon with a local recurrence rate of 55% (the highest of all surgeons) from the higher frequency group. Thus, although this study again demonstrated significant variation in local recurrence rates between individual surgeons, firm conclusions regarding the effect of frequency of rectal cancer resection could not be made.

No study could be found in the English literature which examined whether subspecialty training or frequency of rectal cancer resections has any impact on outcome in rectal cancer.

2.2 Objectives and Hypotheses

The primary objective of this study was to determine if surgeon-related factors, namely colorectal training and frequency of rectal cancer resection, independently predict outcome in rectal cancer. The specific objectives were both descriptively and analytically based.

2.2.1 Descriptive objectives

- To describe the distribution of various potential prognostic variables in a cohort of potentially curable rectal cancer patients.

- To identify the patterns of subspecialty colorectal training and the frequency of rectal cancer surgery among surgeons performing operations for rectal cancer in Edmonton.

2.2.2. Analytic objectives

- To determine if surgical subspecialty training in colorectal surgery and /or frequency of rectal cancer resection by the surgeon is/are independent risk factor(s) for (i) survival, (ii) local recurrence, (iii) perioperative mortality, and/or (iv) postoperative morbidity in rectal cancer surgery.

- To examine the relationship between demographic, preoperative, intraoperative, tumour-specific and adjuvant therapy factors and outcome in rectal cancer.

- To quantify the risk of different prognostic factors on outcome.

2.2.3. A Priori hypotheses

The following hypotheses were established a priori:

- Both colorectal training and higher frequency of rectal cancer resections by surgeons independently improve survival and reduce local recurrence in rectal cancer (primary hypothesis).

- Perioperative mortality and postoperative morbidity are reduced in colorectal-trained surgeons and in surgeons performing a higher frequency of rectal cancer resections.

2.2.4 Research Hypotheses

*1. In rectal cancer, **survival** is improved in patients whose operation was performed by a colorectal-trained surgeon compared with those whose operation was performed by a surgeon with no specific colorectal training.

2. In rectal cancer, **local recurrence** is reduced in patients whose operation was performed by a colorectal-trained surgeon compared with those whose operation was performed by a surgeon with no specific colorectal training.

3. In rectal cancer, **perioperative mortality** is reduced in patients whose operation was performed by a colorectal-trained surgeon compared with those whose operation was performed by a surgeon with no specific colorectal training.

4. In rectal cancer, **postoperative morbidity** is reduced in patients whose operation was performed by a colorectal-trained surgeon compared with those whose operation was performed by a surgeon with no specific colorectal training.

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* Primary null hypotheses

* 5. In rectal cancer, **survival** is improved as the frequency of rectal cancer resections by the surgeon increases.

6. In rectal cancer, **local recurrence** is reduced as the frequency of rectal cancer resections by the surgeon increases.

7. In rectal cancer, **perioperative mortality** is reduced as the frequency of rectal cancer resections by the surgeon increases.

8. In rectal cancer, **postoperative morbidity** is reduced as the frequency of rectal cancer resections by the surgeon increases.

2.3 Relevance of the study

Although a great deal of rectal cancer literature exists, very little deals specifically with surgeon-related factors. The finding of an outcome benefit (i.e. reduced perioperative morbidity, reduced local recurrence, and/or increased survival) in a subgroup of surgeons has far reaching implications, especially in the present health care environment. If, indeed, subspecialty colorectal training improves outcome in rectal cancer, the referral of rectal cancer surgery to centers with fellowship-trained colorectal surgeons would seem justified. Such an approach already has recently been adopted in Sweden where rectal cancer operations are performed by a small select group of surgeons.[146,147] The results of this recent approach have not yet been published.

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* Primary null hypotheses

In addition, the finding of outcome benefit in a subgroup of surgeons would question the perhaps outmoded objective of the general surgeon as a "Jack of all trades". Indeed, subspecialization in general surgery has been an evolving phenomenon over the past twenty years. Specifically with rectal cancer, however, general surgeons may need to adopt a "take it up or give it up" approach, certainly a difficult and professionally threatening proposition.

While most clinical rectal cancer research at present involves the investigation of adjuvant therapy in the hopes of improving survival and decreasing local recurrence, a finding of an outcome benefit in this study would reinforce that the surgical principles of a cancer operation are of significant importance in terms of outcome.

On the other hand, if a study with an adequate statistical power demonstrated that neither colorectal training nor a higher frequency of resections impacts outcome in rectal cancer, the argument for regionalization and subspecialization of services could not be made based on scientific data measuring success rates as an outcome. Indeed, both the practical clinical need for subspecialization and the regionalization of rectal cancer surgery could be questioned.

Chapter 3

Materials and Methods

3.1 Study Design

The study protocol is based on a retrospective cohort design. To allow for a minimum follow-up on patients of 5 years, patients having an operation for rectal cancer from January 1, 1983 to December 31, 1990 inclusive in the Edmonton area were considered eligible for the study. Follow-up of the cohort continued until August 1, 1995.

3.2 Selection of Cohort

3.2.1 Initial selection:

Hospital medical records of all patients admitted to one of the five Edmonton hospitals (University Hospitals, Royal Alexandra, Grey Nuns', Misericordia or Charles Camsell) with a diagnosis of rectal or rectosigmoid carcinoma over the time period of January 1, 1983 to December 31, 1990 were reviewed for potential inclusion. The relevant ICD-9-CM codes (which are used for coding hospital discharge diagnoses) are 154.0 - 154.8 inclusive. Inclusion was based solely on the data from these records, with one exception.*

3.2.2 Inclusion and exclusion criteria:

Records screened using ICD-9-CM codes were then reviewed for potential inclusion in the study.

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* With regards to inclusion criterion #2, occasionally sigmoidoscopic location of the tumour was not documented in the hospital chart. In these cases, office charts of the responsible endoscopist were reviewed to ascertain the distance from the dentate line.

Inclusion criteria:

1. A diagnosis of primary, non-recurrent adenocarcinoma as stated in the pathology report.

2. The most distal portion of the tumour located within 16 cm of the dentate line or within 18 cm of the anal verge on preoperative sigmoidoscopy (flexible or rigid).

3. Initial surgical treatment by low anterior or abdominoperineal resection during the above specified time period.

Exclusion criteria:

1. Initial operation (low anterior or abdominoperineal resection) for recurrent disease.

2. Visceral metastatic disease left unresected at initial operation (TNM Stage 4).

3. Incomplete resection as deemed by carcinoma present at the surgical margin on pathology report.

This cohort includes all patients undergoing potentially curative treatment of rectal cancer in the greater Edmonton area, as all rectal cancer resections would be performed at one of the five aforementioned hospitals. The generalizeability to other geographical areas, particularly rural, as well as the potential for a referral bias, will be discussed in Chapter 7, Section 7.8.

3.3 Sources of Data

A sequential summary of the sources of data used in this study is shown in Figure 3.1, which includes the numbers of patients assessed at each stage. All data were collected by a single investigator (G.P.). Data collection was considered complete once ascertainment was made of all demographic, preoperative, operative, postoperative, pathologic and outcome variables described in sections 3.4.1-3.4.6 of this chapter.

3.3.1 Hospital medical records:

Once a patient met the inclusion criteria, the medical record of the admission for definitive operation was reviewed. From this, demographic, preoperative, operative, and pathology data were collected. In addition, documented postoperative notes/results and length of stay were recorded.

Subsequent hospital admission records, when present, then were used to collect data regarding postoperative notes/results, survival and local recurrence. However, no outcome data regarding survival or local recurrence was sought until demographic, preoperative, operative, and pathology data were complete.

3.3.2 Cross Cancer Institute records:

All patients with histologically confirmed cancer are entered into the Alberta Cancer Registry which is linked to Vital Statistics at Alberta Health. Subsequent death of patients in this registry in the province of Alberta is thus known, as is the cause of death (ICD-9-CM) which appears on the death certificate. All patients in the Alberta Cancer Registry have a chart at the Cross Cancer Institute, although not all of these patients have actually been seen at the Cross Cancer Institute. Thus, all previously identified patients from Section 3.3.1 had a chart at the Cross Cancer Institute. The Registry and chart are updated for death in the province on a monthly basis. In addition, the Registry attempts to obtain information regarding patient status (free of disease, alive with metastasis, lost to follow-up, died) on a yearly basis by written communication with the referring physician.

Cross Cancer Institute charts of all patients included in the study as per Section 3.3.1 of this chapter were identified based on name and birthdate. These charts then were reviewed for data regarding long-term postoperative complications, adjuvant therapy, local recurrence and survival. Review and recording of these data were completed in a blinded fashion on a separate form to limit any potential ascertainment of outcome bias.

3.3.3 Surgeon's office charts

All surgeons' office charts of patients included in the study were reviewed with the exception of patients suffering perioperative mortality or patients with complete data and follow-up after review of their Cross Cancer Institute record. These office charts were used to record data concerning long-term postoperative complications, local recurrence and survival. Specifically, postoperative complications such as wound problems and anastomotic strictures were more likely to be recorded in the surgeon's office record than the Cross Cancer Institute chart. Again, similar blinding as described in Section 3.3.2 was used.

3.3.4 Primary care physician communication

When methods described in sections 3.3.1-3.3.3 yielded incomplete follow-up data, the patient's primary care physician, as documented in the most recent surgeon or Cross Cancer Institute correspondence, received a letter (Appendix 2) requesting follow-up information (Appendix 3). A copy of the Outline of the Study Protocol (Appendix 4) was included in this mail-out as well as a stamped return envelope addressed to one of the investigators (GP) for return of follow-up information. A repeat mail-out was conducted to those primary care physicians where no return correspondence was received within sixty days. If this still was not successful, the individual primary care physicians were contacted by telephone and information was recorded based on verbal response to the specific questions on the Reply Form (Appendix 3).

3.3.5 Direct patient communication

A telephone call to remaining patients with incomplete follow-up data was attempted at their most recently recorded telephone number. If the patient or family member was successfully contacted in this manner, information was recorded based on verbal response to the specific questions on the Reply Form (Appendix 3).

3.3.6 Other agency communication

Incomplete follow-up data remained on a small minority (35 of 683 patients, 5%) following the above procedures. A letter requesting any vital statistical information regarding these patients then was sent to the Provincial Health Departments of British Columbia, Ontario, and Quebec. A similar letter was also sent to the above-mentioned Provincial Cancer Boards regarding available registry information (Appendix 5).

3.3.7 Incomplete observations

Patients without complete follow-up data following these procedures (29 of 683, 4%) were labeled "suboptimal follow-up". Long-term complication data in these patients was labeled "unknown". For the purposes of local recurrence and survival, these patients were treated as censored at the time of the most recent documented physician contact. Twenty of these 29 patients were labeled "unknown" prior to five-year follow-up.

3.4 Procedures and Instruments

A Precoded Data Collection Form was used for all patients (Appendix 6). A summary of all variables and their coding is shown in Appendix 7. Specific details and definitions of certain variables follow.

3.4.1 Preoperative variables

Fixed - documentation preoperatively or intraoperatively of a clinically fixed tumour.

Obstruction - complete large bowel obstruction documented preoperatively and secondary to the rectal tumour.

CEA - preoperative carcinoembryonic antigen level measured in mg/dl. If preoperative adjuvant therapy was used, the CEA level prior to adjuvant therapy was recorded.

Level - preoperative level of the most distal portion of the tumour from the dentate line, as measured on sigmoidoscopic (flexible or rigid) exam. If the anal verge was used as the reference point for the level, 2 cm was subtracted in order to approximate the level from the dentate line.

Goldman number and class - In an attempt to control for preoperative medical illness, each patient received a Goldman Risk Index score and corresponding classification (Appendix 8).[148] This classification has been shown to be predictive of perioperative and postoperative mortality.

3.4.2 Operative variables

Colorectal-trained surgeon - defined as a surgeon with post-General Surgery fellowship training in colorectal surgery.

Surgeon - attending surgeon performing the operation, independent of colorectal training.

Two-teamed approach - In abdominoperineal resections, the presence of a second surgeon performing the perineal dissection.

Intraoperative tumour spill - documentation in the operative and/or pathology report of sharp or blunt dissection through tumour.

Inadvertent perforation of the rectum - documentation on the operative and/or pathology report of full thickness penetration of the rectal wall.

Operative time - time from initial skin incision to dressing application (**not** anaesthetic time).

En bloc resection - resection of other structures in continuity with the rectal resection.

Estimated blood loss - the value reported in the anaesthetic report was used. If it was not recorded in the anaesthetic report, the operative note value was used.

Transfusion - all perioperative transfusions were considered from 48 hours preoperatively to two weeks postoperatively.

3.4.3 Postoperative complications

Perioperative mortality - all deaths from the time of anaesthesia induction to 30 days postoperatively or to hospital discharge from operative admission, whichever is longer.

Pneumonia - this diagnosis must include fever >38.0, respiratory symptoms and chest X-ray consolidation greater than 48 hours postoperatively.

Wound infection (abdominal or perineal) - clinical signs of wound infection with positive cultures.

Perineal sinus - persistent drainage from a non-infected perineal wound at least 3 months postoperatively.

Colostomy complications - any documented colostomy complication requiring operation within one year postoperatively (most often necrosis, prolapse, or hernia)

Anastomotic leak - clinical manifestations (pain, fever, ileus) with documentation of a leak on contrast studies.

Anastomotic stricture - documented postoperative nonmalignant anastomotic stricture on endoscopy or rectal examination.

Abdominal sepsis - presence of postoperative abdominal or pelvic abscess.

Urinary retention - clinical manifestations of urinary retention requiring cystoscopy or voiding cystourethrogram.

Urinary tract infection - symptomatic bacturia $>10^8$ colonies per ml.

Small bowel obstruction - clinical manifestations with radiographic evidence of a mechanical small bowel obstruction (ileus not included).

Length of stay - measured from date of operation to date of discharge.

3.4.4 Pathology

T, N, stage - see Appendix 1. If no lymph nodes found (positive or negative), N=0

Grade - Blenkinsopp et al.[94] classification system (Chapter 1, Section 1.5.2)

Number of lymph nodes - total number lymph nodes examined in pathology specimen.

Proximal, distal margins - measured to the nearest half centimetre on the gross specimen.

Radial margin - if no comment was made in the pathology report, this was considered unknown. Positive radial margin was an exclusion criterion in this study (Section 3.2.2)

Size of tumour - the greatest dimension on the gross specimen, measured to the nearest centimeter.

Distance from dentate line - measured on the gross specimen, to the nearest centimetre (abdominoperineal resection only).

Invasion - microscopic evidence of vascular, neural or lymphatic invasion.

3.4.5 Adjuvant therapy

Type - 5 potential strategies exist:

1. No adjuvant therapy
2. Preoperative radiotherapy
3. Preoperative chemotherapy and radiotherapy
4. Postoperative radiotherapy
5. Postoperative chemotherapy and radiotherapy

- Where applicable, dose of radiotherapy (measured in centigray) and chemotherapy regime are recorded.

3.4.6 Outcome events

Death from any cause.

Disease-specific death - death from rectal cancer.

Overall recurrence - local or metastatic recurrence of rectal cancer.

Local recurrence - any anastomotic, pelvic or perineal tumour confirmed histologically or by CT scan prior to death (autopsy findings not included)

Postoperative complications - as per Section 3.4.3

Perioperative mortality - as per Section 3.4.3

3.4.7 Observation times

Overall survival - from inception to death from any cause

Disease-specific survival - from inception to death from rectal cancer, with non-rectal cancer deaths treated as censored.

Event free survival - from inception to time of overall recurrence.

3.4.8 Follow-up completeness

Follow-up times - measured in months from date of operation to present, to event, or to most recent follow up (if "suboptimal follow-up").

Complete - survival follow-up deemed complete if:

1 - data and cause of death known, or

2 - patient disease-free when seen by physician within the past two years (9/93-9/95) **and** alive according to Alberta Cancer Registry data.

As previously stated, if 1 or 2 were not satisfied, the patients' follow-up data were deemed "suboptimal follow-up". Such follow-up times were determined from last documented patient-physician contact, and cases were considered censored.

3.5 Cut-Point Determination

Several continuous variables were converted to categorical variables for certain analyses. Those continuous variables categorized on the basis of similar approaches employed in the literature included age (<40 years, 40-59 years, 60-79 years, and >80 years), CEA (dichotomized at 5 mg/dl), and level in the rectum (categorized into low, mid, high). The decision to dichotomize the number of resections by the surgeon around the median was made a priori in order to be both clinically meaningful and statistically powerful. Estimated blood loss and operative time were categorized as quartiles after scaling procedures suggested this approach.

3.6 Statistical Methods

Statistical analyses were performed using the statistical software SPSS for Windows.

3.6.1 Univariate analyses

All univariate analyses, whether used as initial exploratory analyses or as final analyses, employed the following tests: [125,149]

i. *t*-tests were used to test the difference between the means of two groups. The F-test was used to test the equality of variances between the two groups. For $p<0.05$, the *t*-test was conducted based on separate variance methods, otherwise, a pooled variance *t*-test was used.

ii. One-way analysis of variance (ANOVA) was used to test the differences in means between three or more groups.

iii. The Chi-square test for categorical data was used to test differences between proportions. If a 2 by 2 table contained a cell count less than 5, Fisher's exact test was used.

iv. The Kaplan-Meier method was used to obtain local recurrence and survival curves. The logrank test was used for univariate analyses of these outcomes. This technique requires the assumption that censoring is a random process and is independent of the endpoint under study. As known predictors of study endpoints were equally distributed among censored and non-censored cases, and as censoring for local recurrence and disease-specific survival was similar, this assumption appeared justified. Because early censoring from loss to follow-up was minimal (3%) and was equally distributed within the predictor variables (colorectal training, frequency of rectal cancer resection), censoring also appears to be independent of study covariates. The only other censoring occurred in the analysis of local recurrence and disease-specific survival in patients who died of causes unrelated to rectal cancer. Again, non-rectal cancer deaths occurred in less than 11% of patients and appeared equally distributed within predictor variables. Thus, the assumption of random censoring appeared justified.

Two-tailed tests were used for the *t*-test. Statistical significance was set at $p < 0.05$. Although many statistical analyses were conducted, the presence of a limited number of *a priori* hypotheses obviated the need to apply a multiple comparisons adjustment to this p-value. P-values will be presented for all analyses.

3.6.2 Multivariate analyses

Three different multivariate analysis techniques were used:

i. *Cox proportional hazards regression* [126,150]

Cox proportional hazards regression was used to determine the adjusted associations of different independent variables with time-related outcomes (local recurrence and survival). The general model is as follows:

$$h_j(t)/h_0(t) = \exp\{\boldsymbol{B}_1X_1 + \boldsymbol{B}_2X_2 + \boldsymbol{B}_3X_3 + ... + \boldsymbol{B}_iX_i\}$$

where $h_j(t)$ is the hazard of the dichotomous outcome at time t, $h_0(t)$ the baseline hazard dependent only on time, B_i the unknown coefficient for the ith independent variable, and a X_i the value of the ith independent variable.

This model is based on the assumption of proportional hazards, that is, that the ratio of the hazards is independent of time. This was tested for all proposed models by plotting a log minus log survival (LML) plot of Kaplan-Meier survival curves for each variable in the final model. If the resultant plots appeared parallel, the proportional hazards assumption was considered justified.

Models were examined by means of manual forward stepwise regression (computer automated "forward regression" was not used) with independent variables and interaction terms entered or removed based on the statistical significance of the likelihood ratio test.[151] A forward rather than backward elimination approach to model building was used as it was more conducive to a manual approach and permitted examination of specific combinations of variables in the model during the model building process believed to be clinically important and defensible. Where independent variables were considered important to the model based on the literature they were included, regardless of their statistical significance.

ii. *Multiple logistic regression* [151]

This technique was used to assess associations of independent variables with various dichotomous outcomes. Whenever appropriate, non-dichotomous outcomes were recoded to dichotomous outcomes in the presence of a skewed distribution, on the basis of previous literature concerning outcome, or based on clinical relevance. The general form for multiple regression models is expressed as follows:

$$\ln (P/[1-P]) = B_0 + B_1X_1 + B_2X_2 + \ldots. B_jX_j + e$$

where P is the probability of the dichotomous outcome. Thus P/(1-P) is the odds of P. B_0 is the coefficient of the constant, with B_j being the coefficient of the j^th^ independent variable, and e the independent random errors. These B_j coefficients also represent the natural logarithms of the odds ratios associated with their respective independent variables.

A similar approach to model building as used for Cox proportional hazards regression was used.

iii. *Multiple linear regression* [151]

This technique was used to examine associations of independent variables with continuous outcome variables. The model is expressed by the following:

$$Y = B_0 + B_1X_1 + B_2X_2 + \ldots. B_jX_j + e$$

where Y is the predicted value of the continuous outcome variable, B_j the coefficient of the j^th^ independent variable, X_j the value of the j^th^ independent variable, and e the independent random errors. Again, a similar approach to model building as previously described was employed.

3.7 Statistical Power and Required Study Size

Using the General Formula for total sample size (based on a univariate analysis),[152] a study size of 560 patients is sufficient to detect differences of 10% in the outcomes between colorectal-trained and non-colorectal-trained surgeons, assuming an outcome rate of 30% in non-colorectal trained surgeons (alpha=0.05(two-tailed); beta=0.20; power=0.80). Egret Sample Size Determination is computer software specifically designed to calculate sample size requirements for Cox regression; 627 patients are necessary to detect a hazards ratio of 1.5 (moderate effect)[153] for the outcome of disease specific survival, adjusting for the estimated confounding of stage and grade, assuming a 10% loss to follow-up, and estimating a control disease-specific survival rate of 50% (two-tailed alpha=0.05; beta=0.10; power=0.90).

In a preliminary census of the five hospitals from which patients were to be recruited, there were approximately 580 patients eligible for this study over the five years 1985-1989. Thus, assuming an 80% true eligibility, it was considered that an appropriate study size would be obtained if patients seen over 8 years, 1983-1990, were studied. It was anticipated that this would result in a study population of 650.

3.8 Data Management

The precoded form for recording data from hospital, office, and Cross Cancer Institute charts is included in Appendix 6. Data was entered into a database management program (dBase IV) on a Pentium 75 personal computer. This input was coded and did not include the patient's name or other hospital identification numbers, but did include a cross-reference number to the original data collection form.

Three methods of data cleaning and verification were used. Initial exploratory descriptive statistics were used to identify any obvious outliers. Secondly, use of a data cleaning program (Data Entry II) was applied to the data in which variable requirements were

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specified and resultant inconsistencies identified. Finally, a systematic manual review of every entered variable, with reference to the precoded data collection form (Appendix 6), was performed on every fifth case. A final systematic review of a random sample of 60 cases identified no errors and thus data quality was considered adequate.

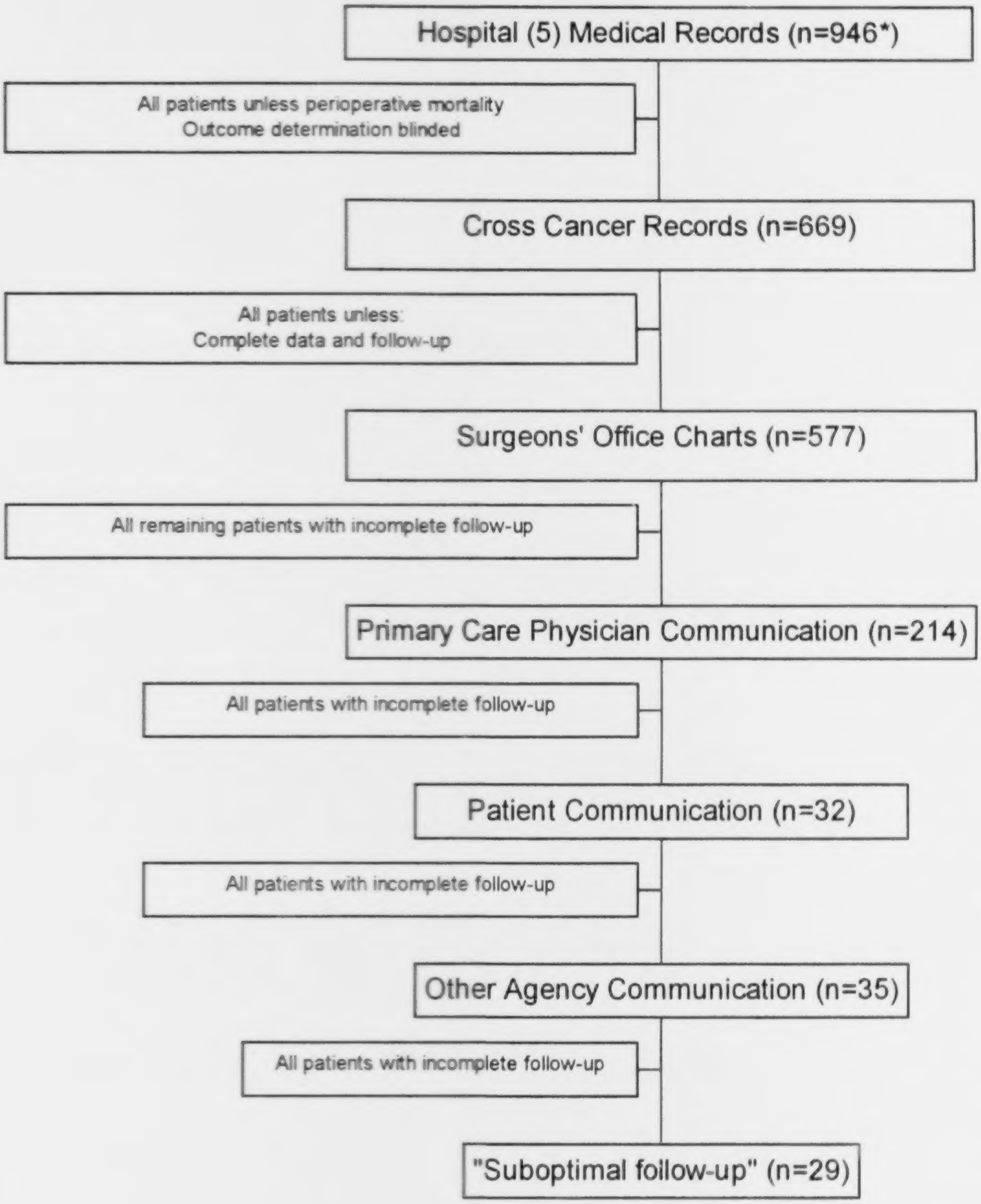
All completed precoded data collection forms have been retained in a locked filing cabinet and will be destroyed at the completion of the study. All data input and analysis were performed on a single personal computer. Data, secured on a computerized file, will be retained for possible audit purposes for seven years after publication. A separate computer file will link each patient record with a name and birthdate.

3.9 Ethical Issues

Ethics approval for this study was obtained from the University of Alberta Ethics Review Committee (Appendix 9). Reciprocal approval from the other hospitals involved in the study was obtained. Similarly, ethics approval and temporary review privileges were obtained from the Cross Cancer Institute. Finally, permission was sought from all surgeons in order to review their office charts (Appendix 10). This permission was granted by all surgeons in practice at the time of the record review.

As this study involved the review and analysis of existing records and data, no informed consent of patients was required by the Ethics committees. Patient names were recorded only on the precoded data forms. No names or institution identification numbers exist on the computer database. In addition, no surgeons' names appear on the database. No analysis have been or will be performed based on individual surgeon performance.

Figure 3.1: Data Sources (n=number of patients)


Hospital (5) Medical Records (n=946*)
All patients unless perioperative mortality
Outcome determination blinded
Cross Cancer Records (n=669)
All patients unless:
Complete data and follow-up
Surgeons' Office Charts (n=577)
All remaining patients with incomplete follow-up
Primary Care Physician Communication (n=214)
All patients with incomplete follow-up
Patient Communication (n=32)
All patients with incomplete follow-up
Other Agency Communication (n=35)
All patients with incomplete follow-up
"Suboptimal follow-up" (n=29)

* - 683 patients met eligibility criteria

Chapter 4

Results: Descriptive

Of the 683 patient records included in this study, 29 (4.2%) were censored owing to loss to follow-up. Total observation times ranged from 2 to 152 months with a median follow-up of 84 months (mean 81.3 months). Follow-up for at least 5 years and as long as 12.7 years was available on 663 (97.0%) of all patients. The full data set was able to be utilized in all analyses of local recurrence, survival and perioperative mortality.

As a preliminary to the deeper analytic findings of this study, some simple descriptive results are presented in this chapter. These describe the study cohort in terms of demographic, preoperative, and operative characteristics. In addition, tumour characteristics and the use of adjuvant therapy in the study cohort are described. Finally, outcome rates, in terms of local recurrence, survival, perioperative mortality and postoperative morbidity, are presented.

4.1 Demographic and Preoperative Variables

Demographic and preoperative characteristics are presented in Table 4.1 for the 683 patient records included in the study. Sixty-one percent were male and the mean age was 65 years. The majority of patients (90%) were of a preoperative Goldman Class 1 or 2 suggesting that most patients were not high risk surgical candidates. The level of the rectal tumours was relatively evenly distributed among low, middle, and high. Preoperative CEA measurements were available in only 409 (60%) patients. Although of potential prognostic value, the preoperative CEA does not alter management in any way, thus explaining why many patients did not have this test performed.

4.2 Operative Variables

Operative variables are shown in Table 4.2. Sixteen percent of patients had operations performed by colorectal-trained surgeons, although only 5 of the 53 (9%) surgeons involved in the study were colorectal-trained. The relationship between colorectal-training and frequency of rectal cancer resection is further examined in Chapter 5, Section 5.1. Intraoperative tumour spill and inadvertent perforation of the rectum was seen in 13.5% and 12.4% of patients respectively. Sixty-five percent of patients received perioperative blood transfusions. APR was performed in 43.8% and LAR in 56.2%. In patients undergoing LAR, 57.3% had a stapled anastomosis. A two-teamed approach of APR was used in the majority of cases (68.6%).

The breakdown of number of resections (total and per year) by the surgeon, irrespective of colorectal training, is shown in Table 4.3. Among all patients, 52.7% had operations by surgeons performing a minimum of 21 procedures over the study period, while 47.3% of patients were treated by surgeons performing <21 procedures over the study period. To account for the specific experience of surgeons who retired or began practice during the study period 1983-1990, the number of rectal cancer resections **per year** by each surgeon was calculated by dividing the total number of resections performed by the number of years over the study period that the surgeon was in practice (Table 4.3). The identical 52.7% of patients who had their operations by surgeons who performed ≥ 21 resections over the study period also had their operations by surgeons performing ≥ 2.6 resections per year. Thus, all subsequent analyses presented of frequency of rectal cancer resections include only the total number of resections over the study period as the results of the analogous analyses of number of resections per year were identical.

4.3 Tumour Characteristics

Tumour characteristics identified at pathological examination are shown in Table 4.4. More than one-third (37.6%) of the patients had lymph node spread at operation. As expected, the majority of the tumours (80.2%) were moderately differentiated. A distal resection margin less than 2 cm, widely considered to be inadequate, was found in 110 (16.1%) patients. The status of the radial resection margin was unknown in 2.8% indicating an incomplete pathology report (a positive radial margin was an exclusion criterion, see Chapter 3, Section 3.2.2). Most tumours (87.6%) were adenocarcinomas not otherwise specified.

4.4. Adjuvant Therapy

Several different adjuvant therapy strategies were used in the cohort and are presented in Table 4.5. Of note is that only 237 (35.4%) patients received any type of adjuvant therapy. The mean dose in patients who received radiotherapy was 4,308 cGy (SD = 1,042) with a median dose of 4,500 cGy. In patients who received chemotherapy, 5- Fluoro-uracil was used alone in 28 (63.6%) patients, in combination with Levamisole in 9 (20.5%) patients, in combination with Follinic Acid in 5 (11.4%) patients, and in combination with other agents in 2 (4.5%) patients. It is noteworthy that Levamisole was not accepted as a standard agent for rectal cancer until the late 1980s, thus explaining its limited use in this study.

4.5 Outcomes - Survival and Local Recurrence

Table 4.6 shows crude and Kaplan-Meier overall survival, disease-specific survival, event-free survival, and local recurrence rates. Crude rates are simply the number of events divided by the study population (N=683). Five-year rates are shown as well, for the purposes of comparison to the literature (Chapter 7, Sections 7.2 and 7.3). Of note is that of the 375 patients who died during the study, 73 (19.5%) died of causes unrelated to their rectal cancer. As mentioned in Chapter 3, these were treated as censored cases in the determination of disease-specific survival, event-free survival, and local recurrence rates.

4.6 Outcomes - Operative Complications and Mortality

Perioperative mortality (as defined in Chapter 3, Section 3.4.3) occurred in 14 (2.0%) patients. Complications are presented in Table 4.7 and are broadly categorized as generic, APR-specific, and LAR-specific. Unfortunately, ascertainment of presence of some long-term complications (perineal sinus, colostomy complication requiring operation, and anastomotic stricture) was not possible in some cases and thus these are listed as unknown in Table 4.6.

The presence of ≥ 1 generic postoperative complication was identified in 177 (26.5%) of patients. This was largely a result of the high rate of abdominal wound infection observed (14.2%).

Of the 16 patients with anastomotic leaks following LAR, 6 (37.5%) required reoperation while 10 (62.5%) were treated successfully nonoperatively with antibiotics and bowel rest. Only 7 of the 41 patients (17.1%) with an anastomotic stricture following LAR required operative revision, with the remainder treated by endoscopic or manual dilatation. The mean length of stay in hospital was 15.5 days (SD=9.6) with a median length of stay of 13 days.

Table 4.1. Demographic and preoperative characteristics of the study cohort, n = 683

Sex, n (%)		
Female	264	(38.7)
Male	419	(61.3)
Age (yrs) at operation - mean (SD), median	65.1	(11.78), 65
Hospital of operation, n (%)		
University	192	(28.1)
Royal Alexandra	183	(26.3)
Grey Nuns	125	(18.3)
Miseracordia	145	(21.2)
Charles Camsell	38	(5.6)
Preoperative complete obstruction, n (%)		
Yes	40	(5.9)
No	643	(94.1)
Preoperative tumour fixation, n (%)		
Yes	50	(7.3)
No	633	(92.7)
Goldman class, n (%)		
1	411	(60.2)
2	206	(30.2)
3	66	(9.7)
Tumor level, n (%)		
Low	168	(24.6)
Mid	266	(38.9)
High	249	(36.5)
Preoperative CEA (mg/dl) - mean (SD), median *	14.2	(53.4), 3.6

* n = 409

Table 4.2. Operative characteristics of study cohort, n = 683

Colorectal-trained surgeon, n (%)		
Yes	109	(16.0)
No	574	(84.0)
Operative time, min. - mean (SD), median	156	(51), 150
Estimated blood loss, ml - mean (SD), median	830	(675), 700
Perioperative transfusion, n (%)		
Yes	441	(64.6)
No	242	(35.4)
Inadvertent tumour spill, n (%)		
Yes	92	(13.5)
No	591	(86.5)
Inadvertent perforation of the rectum, n (%)		
Yes	85	(12.4)
No	598	(87.6)
Operative procedure, n (%)		
Abdominoperineal resection (APR)	299	(43.8)
Low anterior resection (LAR)	384	(56.2)
If LAR, type of anastomosis, n (%)		
Handsewn	166	(42.7)
Stapled	220	(57.3)
If APR, two-team approach, n (%)		
Yes	205	(68.6)
No	94	(13.8)

Table 4.3 Number resections (total and per year) by surgeon for the study cohort (n=683)

Number resections, total	
Mean (SD)	20.9 (11.5)
Median	21
Range	1-48
Cases with surgeons performing ≥ 21 resections, n (%)	360 (52.7)
Cases with surgeons performing < 21 resections, n (%)	323 (47.3)
Number resections, per year	
Mean (SD)	2.8 (1.5)
Median	2.6
Range	0.2-6.0
Cases with surgeons performing ≥ 2.625 resections (per year), n (%)	360 (52.7)
Cases with surgeons performing < 2.625 resections (per year), n (%)	323 (47.3)

Table 4.4 Tumour characteristics in study cohort, n = 683

Stage (TNM), n (%)		
1	140	(20.5)
2	286	(41.9)
3	252	(36.9)
4 [S]	5	(0.7)
Grade, n (%)		
Well differentiated	57	(8.3)
Moderately differentiated	548	(80.2)
Poorly differentiated or anaplastic	78	(11.4)
Distal margin within 2 cm., n (%)		
Yes	110	(16.1)
No	573	(83.9)
Radial margin status, n (%)		
Negative	664	(97.2)
Unknown	19	(2.8)
Vascular or neural invasion, n (%)		
Yes	108	(15.8)
No	575	(84.2)
Histological type, n (%)		
Adenocarcinoma	598	(87.6)
Mucinous	85	(11.0)
Signet ring	7	(1.0)
Other	3	(0.4)
Tumor size, cm - mean (SD), median	4.4	(1.8), 4.0

[S] - Synchronous liver resection for metastatic disease

Table 4.5 Adjuvant therapy strategies in study cohort, n = 683

	n	%
No adjuvant therapy	432	64.6
Adjuvant therapy	237	35.4
Preoperative radiotherapy only	50	7.5
Preoperative radiotherapy and chemotherapy	18	2.7
Postoperative radiotherapy	143	21.4
Postoperative radiotherapy and chemotherapy	26	3.8

Table 4.6 Survival and local recurrence rates for the study cohort

	Crude (%)	Kaplan-Meier (%)	5-Year K-M (%)
Local Recurrence	30.5	33.8	33.2
Event-Free Survival	51.1	47.8	50.2
Disease-Specific Survival	54.9	46.3	59.0
Overall Survival	43.0	31.1	54.6

K-M: Kaplan-Meier method

Table 4.7 Surgical complications in the study cohort*

Complication Type	n	%
Generic Complications (n=669)		
Pneumonia	40	6.0
Abdominal wound infection	95	14.2
Abdominal wound dehiscence	12	1.8
Abdominal sepsis	20	3.0
Small bowel obstruction not requiring laparotomy	39	5.8
Small bowel obstruction requiring laparotomy	13	1.9
Presence of ≥ 1 generic complication(s)	177	26.5
APR-Specific Complications (n=293)		
Perineal wound infection	74	25.3
Perineal sinus	62	21.2
Perineal sinus - unknown	32	11.0
Colostomy complications requiring operation	26	9.9
Colostomy complications requiring operation - unknown	34	11.6
Presence of ≥ 1 APR-specific complication(s)	115	39.2
LAR-Specific Complications (n=376)		
Anastomotic leak	16	4.3
Anastomotic stricture	41	10.9
Anastomotic stricture - unknown	44	11.7
Presence of ≥ LAR-specific complication(s)	52	13.8

* perioperative mortality patients excluded

Chapter 5

Results: Univariate Analysis

Initial exploratory analysis and examination of several specific relationships was performed using univariate techniques. This chapter describes the association between colorectal surgical training and total number of resections performed and also examines the association between potential predictor variables and surgeon-related characteristics. Finally, a univariate analysis of outcome measures is presented.

5.1 Association Between Colorectal Training and Total Number of Resections Performed

As surgical colorectal training and the total number of resections performed by the surgeon were critical to later hypothesis testing, further examination of their association was performed (Table 5.1a). Of the 52 surgeons involved in the study, 5 were colorectal-trained by the criteria described in Section 3.4.2, Chapter 3. Among these 5 surgeons, 3 were also found to have performed ≥ 21 resections during the study period. This finding suggested, not surprisingly, that colorectal-trained surgeons were more likely to perform ≥ 21 resections than their non-colorectal-trained counterparts ($p=0.05$). Of the 2 colorectal-trained surgeons who performed <21 resections over the study period, one performed 19 resections and the other only began practice in 1990 and thus accounted for just 2 patients in the study cohort.

Consequently, patients of colorectal-trained surgeons were much more likely to have had their operation performed by a surgeon who performed ≥ 21 resections over the study period, as shown in Table 5.1b ($p<0.001$). Despite a rather even distribution of patients among surgeons performing <21 or ≥21 resections (47.3% vs 52.7% respectively), greater than 80% of patients of colorectal-trained surgeons were also patients of surgeons who performed ≥ 21 rectal cancer resections.

5.2 Associations with Surgeon-Related Characteristics

Crosstabulations of demographic, preoperative and operative variables according to training of surgeon are presented in Tables 5.2 and 5.3. There was no statistically significant association between surgical training and demographic or preoperative characteristics except for a trend towards low- and mid-level tumours in patients of colorectal-trained surgeons (70.6%) compared with non-colorectal-trained surgeons (62.8%) . With regard to operative variables, colorectal-trained surgeons were much more likely to perform a LAR (72.5%) than their non-colorectal-trained counterparts (35.1%). This is interesting to observe, especially as colorectal-trained surgeons managed a higher proportion of low-level tumours. This relationship is further examined in Table 5.4 which shows that colorectal-trained surgeons performed a LAR, thus preserving the anal sphincter, in 61.0% of patients with low-level or mid-level tumours, compared with non-colorectal-trained surgeons who performed LAR in only 25.8% of such patients. No patients in either group with high rectal tumours underwent APR. Preservation of the anal sphincter, which obviates the need for a colostomy, is more functional and aesthetic for the patient. Colorectal-trained surgeons were also more likely to perform a stapled anastomosis during LAR than non-colorectal trained surgeons. As it is generally possible to perform a lower anastomosis with a stapler than by a handsewn technique, some of the disparity in the operative procedure performed between the two groups of surgeons may be explained by comfort level of the surgeon with the stapler.

Patients of colorectal-trained surgeons were significantly less likely to receive a perioperative blood transfusion (Table 5.3). Although this may be explained by differences in threshold for transfusion between the two surgeon types, the finding of a statistically significant reduction in blood loss in patients of colorectal-trained surgeons suggests that technical operative factors were, at least in part, responsible. Additionally, the finding of a trend, albeit not statistically significant, towards a higher incidence of inadvertent perforation of the rectum in patients of non-colorectal trained surgeons (13.2%) compared with those of colorectal trained surgeons (8.3%) suggests a difference in technical operative factors.

Similarly, Table 5.5 examines associations of tumour characteristics and the use of adjuvant therapy according to surgical training. There are no significant differences in stage, grade, type, size, or invasion of tumour between colorectal-trained and non-colorectal-trained surgeons. Although not statistically significant, a trend towards suboptimal distal resection margins was seen in non-colorectal-trained surgeons ($p=0.06$). There was no significant difference in the use of adjuvant therapy between the two groups of surgeons.

From Tables 5.2-5.5, it appears that traditional prognostic indicators such as tumour stage, grade, size, and type were equally distributed among colorectal-trained and non-colorectal-trained surgeons. However, despite treating a greater proportion of the more difficult low tumours, colorectal-trained surgeons appeared to display technical superiority, as measured by reduced blood loss, fewer perioperative blood transfusions, and a greater likelihood of preserving the anal sphincter.

Similar univariate analyses were performed of demographic, preoperative, and operative variables, for total number of resections performed by the surgeon. There were no significant differences in demographic or preoperative characteristics between the two groups (Table 5.6). Notably, the observed difference in tumour level seen with colorectal training was not observed according to number of resections performed by the surgeon suggesting there is not a trend towards the more of the more difficult lower level tumours being treated surgeons performing ≥ 21 resections. In terms of operative variables (Table 5.7), there was a statistically significant association between surgeons performing <21 resections and longer operating time. As was noted with non-colorectal-trained surgeons, patients of surgeons performing < 21 resections had a significantly higher estimated blood loss and an increased use of perioperative blood transfusions. Similar to colorectal training, these findings suggested a difference in technical proficiency among surgeons performing ≥ 21 resections compared with surgeons performing < 21 resections.

A higher proportion of patients of surgeons performing ≥ 21 resections underwent LAR (61.1%) than patients of surgeons performing <21 resections (50.8%), which was similarly seen with colorectal training (Table 5.7). However, there were no differences noted in anastomotic technique or tumour level between the two groups.

Table 5.8 examines associations between tumour characteristics as well as the use of adjuvant therapy, and the total number of resections by the surgeon. Again, there were no significant differences in stage, grade, type, size, or invasion between the two groups of surgeons. As was seen with colorectal-trained surgeons, patients of surgeons performing ≥21 resections over the study period were less likely to have distal resection margins < 2 cm, which are widely felt to be suboptimal, although this failed to reach statistical significance.

Overall, the type of rectal cancer patient treated by higher and lower frequency surgeons appeared similar, and specifically, the difference in tumour level observed among colorectal-trained and non-colorectal trained surgeons was not found in patients of higher and lower frequency surgeons. However, as was noted with colorectal training, several operative variables (blood loss, transfusion use, operative time) in patients of surgeons performing ≥ 21 resections were improved and a greater propensity to preserve the anal sphincter was found.

5.3 Associations with Local Recurrence and Disease-Specific Survival

As stated in Materials and Methods (Chapter 3), disease-specific survival involves only deaths attributable to rectal cancer, and thus other exits, such as deaths from other causes and loss to follow-up, were treated as censored. Table 5.9 shows several demographic and preoperative variables to be associated with lower disease-specific survival on univariate analysis. These include increasing age, obstruction, increasing Goldman Class, lower tumour level, and CEA ≥ 5.0 mg/dl.

Having the operation performed by a non-colorectal-trained surgeon and a surgeon performing < 21 resections over the study period were associated with decreased disease-specific survival (Table 5.10). The 2 x 2 table of disease-specific survival rates, stratified by colorectal training and number of resections by the surgeon, is shown in Table 5.11a. It is noteworthy that there appeared to be no significant interaction between these two variables;

that is, improvement in disease-specific survival seen in patients where the surgeon was both colorectal-trained and performed ≥ 21 resections (67.3%) compared with patients whose surgeon was neither colorectal-trained nor performed <21 resections (39.2%) was approximately equal to the individual effects of the colorectal trained surgeon and the surgeon performing ≥ 21 resections. This implied that the effect of each of these two surgeon-related factors was independent of the other factor.

Figures 5.1 and 5.2 show Kaplan Meier curves of disease-specific survival stratified for colorectal training and number of resections by the surgeon respectively. In both graphs, the divergent curves are similar in shape with initial separation beginning at approximately 2 years. As expected, the slopes of the curves are greatest over the initial 4 years with few events noted after 5 years. Finally, on visual inspection, the two curves do not cross, indicating that the proportional hazards assumption required for future multivariate analyses is likely valid. Figure 5.3 combines surgical training and frequency of resection, as examined in Table 5.11a, in showing Kaplan-Meier curves for three surgeon groups.

Other operative variables found to be associated with decreased disease-specific survival included the use of perioperative transfusions, inadvertent rectal perforation or intraoperative tumour spill (grouped into a single variable due to high correlation and biologic reasons), and use of an enbloc resection (Table 5.10). Although not linear in association, there appeared to be a significant association between increased estimated blood loss and decreased disease-specific survival.

The data were next analyzed with local recurrence as the endpoint of interest (Tables 5.9 and 5.10). As found with disease-specific survival, obstruction, increasing Goldman Class, and CEA $\geq$ 5.0 mg/dl were associated with local recurrence, although age and level were no longer significant. For immunologic reasons, older patients may have been more prone to suffer distant metastasis and thus more likely to die of metastatic disease. Systemic immune function, however, may have less effect on local recurrence. It was somewhat surprising that tumour level was not associated with local recurrence on univariate analysis. However, as shown in Section 5.2 of this chapter, colorectal-trained surgeons operated on more low-level tumours than non-colorectal-trained surgeons.

As was observed in the analysis of disease-specific survival, the presence of a non-colorectal-trained surgeon and presence of a surgeon performing < 21 resections were again found to be associated with higher local recurrence (Table 5.10). Table 5.11b again illustrates that there does not appear to be any interaction between these two variables and the outcome of local recurrence.

Kaplan-Meier curves are seen in Figures 5.4 and 5.5 for the outcome of local recurrence, stratified by colorectal-training and number of resections by the surgeon respectively. Both graphs again show similarly shaped, divergent curves. In contrast to disease-specific survival, this separation initially appeared in the first year and progressively increased with time. This was expected as local recurrence characteristically occurs within the first two years of the operation and thus differences between surgeon types would be expected to be seen during this interval. The shallow slope of the curves after 2 years further illustrated this fact. The proportional hazards assumption again appears valid for both the colorectal-trained and number of resections variable based on visual examination of the curves.

As was noted with disease-specific survival, perioperative transfusion, inadvertent rectal perforation or intraoperative tumour spill, and use of an enbloc resection were associated with increased local recurrence (Table 5.10).

The impact of tumour-related factors on the outcomes of disease-specific survival and local recurrence was then examined in Table 5.12. Stage, grade, neural/vascular invasion and tumour type were statistically significant in their association with both disease-specific survival and local recurrence. Distal resection margins less than 2 cm and unknown radial resection margin status only appeared to be significantly associated with local recurrence. From a pathophysiologic perspective, close resection margins are likely detrimental by implantation and subsequent growth on another surface, resulting in local recurrence. Although the majority of patients with local recurrence from rectal cancer eventually die of their disease, causative factors for local recurrence are not necessarily associated with disease-specific survival.

Interestingly, although the use of adjuvant therapy is significantly associated decreased disease-specific survival, its univariate association with local recurrence is more complex with preoperative adjuvant therapy having lower local recurrence rates and postoperative adjuvant therapy having the highest rates (Table 5.13). Three different classification strategies were used in examining the association of adjuvant therapy. These alternative classifications of adjuvant therapy suggested that, by univariate analysis: (1) it was postoperative adjuvant therapy that was associated with lower disease-specific survival, and (2) there was a large difference in the associations of preoperative and postoperative adjuvant therapy on local recurrence. For these reasons, Classification 3 will be used for future multivariate analysis as there were a reasonable number of patients in each group and it provides clinically meaningful distinctions. This will be further examined by multivariate techniques in Chapter 6.

It must be emphasized that the associations with local recurrence and disease-specific survival presented in this chapter are univariate. Further, more conclusive, evaluation of the prognostic implications of these factors, controlling for potential confounding and interaction factors by multivariate analysis, is presented in Chapter 6.

5.4 Associations with Perioperative Mortality

There were 14 cases of perioperative mortality for an overall rate of 2%. Table 5.14 shows that only age and Goldman Class were significantly associated with perioperative mortality. This was not unexpected as Goldman Class is a valid measure of risk of perioperative cardiac mortality. Of note is that the correlation between age and Goldman Class was strong ($r = 0.56$, $p < 0.001$). Age, dichotomized at 70 years, is a major component of the Goldman Class (Appendix 8), explaining this significant correlation. On further examination of these two variables at a multivariate level, it would not be unexpected to find that only one is an independent risk factor for perioperative mortality. This will be performed in Chapter 6.

No operative factors were significantly associated with perioperative mortality (Table 5.15). Specifically, neither colorectal training nor number of resections by the surgeon were statistically significant in their univariate association with perioperative mortality. However, a non-significant trend was noted with a higher perioperative mortality rate in patients of non-colorectal-trained surgeons (2.3%) compared with those of colorectal-trained surgeons (0.9%). The power in this analysis was limited at only 28% because of the low perioperative mortality rate. A similar observation for the association with perioperative blood transfusions, where a non-statistically significant trend towards increased perioperative mortality in patients who received transfusions, was observed.

5.5 Associations with Generic, LAR-Specific and APR-Specific Complications

For the purposes of this study, postoperative generic complications included pneumonia, abdominal wound infection, abdominal wound dehiscence, abdominal sepsis, and small bowel obstruction and thus these were tabulated by co-variates. Univariate associations of generic complications according to demographic and preoperative factors are shown in Table 5.16. Significant associations were found between the occurrence of at least one generic complication and increasing age. A dose-response type of relationship was found here with only 6.7% of patients <40 years suffering a generic complication compared with 36.4% of patients ≥ 80 years. A higher rate of generic complications was also noted in patients with low-level tumours (36.0%) versus mid (24.2%) or high (22.4%) tumours suggesting the increased technical difficulty in resection of low rectal tumours may have contributed to the incidence of postoperative complications.

In terms of operative factors (Table 5.17), colorectal-trained surgeons had a significantly lower generic complication rate (15.7%) than non-colorectal-trained surgeons (28.5%) suggesting that the suspected technical differences between the two groups influencing tumour behavior also influences the likelihood of complications. The hypothesis that technical factors played a causative role in the development of these complications was supported by the observation of significantly higher generic complication rates associated with blood transfusion use and greater blood loss. Moreover, differences in postoperative care may account for some of these differences. Of note was that the association between generic complications and the number of rectal cancer resections by the surgeon was not statistically significant.

It is noteworthy that generic complications were seen more frequently following APR (32.8%) than following LAR (21.5%). However, this association possibly represented a confounding effect as operative procedure is strongly associated with both tumour level and colorectal training, as previously demonstrated.

Males had a higher rate of at least one LAR-specific complication (anastomotic leak or stricture) compared with females (19.2% vs. 11.4% respectively, Table 5.18). Again, this could be explained by technical factors. The male pelvis is narrower than the female pelvis and consequently an anastomosis in the more confined narrow male pelvis is more difficult. No other demographic or preoperative factors were associated with LAR-specific complications.

The rate of LAR-specific complications appeared similar among colorectal-trained (15.8%) and non-colorectal-trained (15.3%) surgeons (Table 5.19). This similarity was found despite a more liberal use of LAR among colorectal-trained surgeons, especially for lower rectal tumours (Chapter 5, Section 5.2). This suggested that this more liberal approach towards LAR, in which many colostomies are avoided, was not at the expense of more anastomotic complications. Surgeons performing ≥ 21 resections had a lower rate of LAR-specific complications (11.5%) compared with surgeons performing < 21 resections (21.4%). Although surgeons who performed ≥ 21 resections preferentially performed a higher proportion of LAR, the association of this approach with lower level tumours was not observed. Thus, the decreased LAR-specific complication rate in surgeons who performed ≥ 21 resections again may reflect a difference in technical skill. Of note is no significant association was found between the technique of anastomosis (stapled vs. handsewn) and the occurrence of these complications.

APR-specific complications were defined in this study as to include colostomy complications, perineal infections, and perineal sinuses. No demographic or preoperative factors were found to be significantly associated with the occurrence of ≥ 1 of these complications (Table 5.20). As opposed to LAR-specific complications, the narrow male pelvis likely plays little role in APR-specific complications as the majority of these complications occur in the perineum, not the pelvis.

Colorectal-trained surgeons had a markedly lower APR-specific complication rate (14.8%) than non-colorectal-trained surgeons (42.3%) (Table 5.21). A similar association was seen with surgeons performing ≥ 21 resections (28.2%) compared with those performing < 21 resections (50.8%). Perineal wound healing likely plays a large role in the development of perineal wound infections and sinuses, and thus technical differences in management of the perineal wound among surgeons may account for some of the differences in complication rates observed. This is further supported by the finding of significant association between other factors affecting perineal wound healing, such as inadvertent rectal perforation/tumour spill and primary perineal closure, and APR-specific complications. Specifically, inadvertent rectal perforation potentially permits access of colonic bacteria to the perineal wound, thus predisposing to perineal infection and subsequent slowed wound healing. Absence of a primary perineal closure may also slow wound healing.

5.6 Associations with Length of Stay

The final measure of postoperative morbidity was length of stay in hospital, as measured in days. Excluding cases of perioperative mortality, the mean length of stay for the study cohort was 15.4 days (SD = 9.0) with a range of 5 to 92 days. For the univariate analyses, associations between length of stay and various other factors were determined using length of stay as a continuous variable.

Demographic and preoperative factor associations with length of stay are presented in Table 5.22. Increased Goldman Class and advanced age were associated with longer length of stay suggesting, not unexpectedly, that older patients with more medical problems tended to stay in hospital longer. Patients with fixed tumours and low-level tumours were also associated with significantly longer length of stay.

Both patients of colorectal-trained surgeons and those of surgeons performing ≥ 21 resections were found to associated with shorter length of stay (Table 5.23). Several other operative factors were observed to be statistically associated with longer length of stay on univariate analysis as well. These included longer operative time, greater blood loss, the use of perioperative transfusions, and APR. Clinical interpretation of these findings is difficult as there are likely many confounding effects present. Multivariate analysis (Chapter 6) should aid in differentiating these confounding effects with independent risk factors.

Clinically, it may be argued that the association of factors with prolonged length of stay may be largely related to their association with postoperative complications. For example, in the previous section, associations with generic complications were examined. As shown in Table 5.24, the mean length of stay if there were no generic complications was 13.3 days versus 21.5 days if there was ≥ 1 generic complication. This strong association suggests that factors causing complications are likely associated with longer length of stay. However, in repeating the analysis of Tables 5.22 and 5.23 **excluding** patients with generic complications, all associations persisted with the exception of fixation which was no longer significantly associated with length of stay ($p = 0.94$). This suggests that, with the exception of tumour fixation, associations of factors with prolonged length of stay were not simply explained by their association with generic complications.

Table 5.1 Association between colorectal training and total number of resections performed

A: By Surgeon (n=52)

	< 21 Resections	≥ 21 Resections	Total
Non-Colorectal-trained	37 (78.7%)	10 (21.3%)	47
Colorectal-trained	2 (40.0%)	3 (60.0%)	5
Total	39 (75.0%)	13 (25.0%)	52

$p = 0.05$ (Fisher exact test)

B: By Patient (n=683)

	< 21 Resections	≥ 21 Resections	Total
Non-Colorectal-trained	302 (52.6%)	272 (47.4%)	574
Colorectal-trained	21 (19.3%)	88 (80.7%)	109
Total	323 (47.3%)	360 (52.7%)	683

$p<0.001$ (chi-square)

Table 5.2 Demographic and preoperative variables according to surgeons' training

	Non-colorectal-trained (n=574)		Colorectal-trained (n=109)		p value [P]
Demographic					
Gender					0.85
female	221	(38.5%)	43	(39.4%)	
male	353	(61.5%)	66	(60.6%)	
Age	65.0	(12.0)*	65.7	(10.8)*	0.60
Preoperative					
Obstruction	33	(5.7%)	7	(6.4%)	0.78
Fixation	42	(7.3%)	8	(7.3%)	0.99
Goldman Class					0.87
1	346	(60.3%)	65	(59.6%)	
2	174	(30.3%)	32	(29.4%)	
3	54	(9.4%)	12	(11.0%)	
Level					<0.001
low	151	(26.3%)	17	(15.6%)	
mid	206	(35.9%)	60	(55.0%)	
high	217	(37.8%)	32	(29.4%)	
CEA (mg/dl)	13.2	(35.2)*	18.3	(96.2)*	0.44

* : Continuous variables shown as mean (SD)

[P] : p value for test comparing patients of non-colorectal-trained to those of colorectal-trained surgeons

Table 5.3 Operative variables according to surgeons' training

	Non-colorectal-trained (n=574)		Colorectal-trained (n=109)		p value [P]
Operative time (min.)	156	(55)*	158	(48)*	0.70
Estimated blood loss (ml)	851	(694)*	716	(552)*	0.05
Perioperative transfusion	385	(67.1%)	56	(51.4%)	0.002
Intraoperative tumour spill	81	(14.1%)	11	(10.1%)	0.26
Inadvertent rectal perforation	76	(13.2%)	9	(8.3%)	0.15
Operative procedure					<0.001
LAR	305	(35.1%)	79	(72.5%)	
APR	269	(46.9%)	30	(27.5%)	
If LAR - stapled anastomosis	149	(48.9%)	71	(89.9%)	< 0.001
If APR - two-teamed	187	(69.5%)	18	(60.0%)	0.29

* : Continuous variables shown as mean (SD)

[P] : p value for test comparing patients of non-colorectal-trained to those of colorectal-trained surgeons

Table 5.4 Operative procedure performed for mid- and low-level tumors according to surgical training (n=434)

	APR	LAR	Total
Non-Colorectal-Trained	265 (74.2%)	92 (25.8%)	357
Colorectal-Trained	30 (39.0%)	88 (61.0%)	77
Total	295 (68.0%)	139 (32.0%)	434

$p < 0.001$ (chi-square)

APR: abdominoperineal resection

LAR: low anterior resection

Table 5.5 Tumour characteristics and use of adjuvant therapy according to surgeons' training

	Non-colorectal-trained (n=574)		Colorectal-trained (n=109)		p value [P]
Stage					0.92
1	118	(20.6%)	22	(20.2%)	
2	243	(42.3%)	43	(39.4%)	
3	209	(36.4%)	43	(39.4%)	
4 [S]	4	(0.7%)	1	(0.9%)	
Grade					0.15
well differentiated	43	(7.5%)	14	(12.8%)	
moderately differentiated	463	(80.7%)	85	(78.0%)	
poorly differentiated	68	(11.8%)	10	(9.2%)	
Distal margin < 2 cm	99	(17.2%)	11	(10.1%)	0.06
Radial margin status unknown	19	(3.3%)	0	(0%)	0.06
Vascular/neural invasion	90	(15.7%)	18	(16.5%)	0.83
Signet ring or mucinous	73	(12.7%)	12	(11.0%)	0.62
Size (cm)	4.4	(1.8)*	4.3	(1.7)*	0.56
Adjuvant therapy used	200	(35.7%)[a]	37	(34.3%)[b]	0.78

* : Continuous variables shown as mean (SD)

[P] : p-value for test comparing patients of non-colorectal-trained to those of colorectal-trained surgeons

[S] : Synchronous liver resection for metastatic disease

[a] : n=561 (perioperative mortality cases excluded)

[b] : n=108 (perioperative mortality cases excluded)

Table 5.6 Demographic and preoperative variables according to total number of resections by the surgeon during the study period

	< 21 resections (n=323)		≥ 21 resections (n=360)		p value [P]
Demographic					
Gender					.54
female	121	(37.5%)	143	(39.7%)	
male	302	(62.5%)	217	(60.3%)	
Age	65.3	(12.1)*	64.9	(11.5)*	0.75
Preoperative					
Obstruction	15	(4.6%)	25	(6.9%)	0.20
Fixation	23	(7.1%)	27	(7.5%)	0.85
Goldman Class					0.68
1	195	(60.4%)	216	(60.0%)	
2	100	(31.0%)	106	(29.4%)	
3	28	(8.7%)	38	(10.6%)	
Level					0.29
low	82	(25.4%)	86	(23.9%)	
mid	133	(41.2%)	133	(36.9%)	
high	108	(33.4%)	141	(39.2%)	
CEA (mg/dl)	12.5	(31.4)*	15.7	(66.9)*	0.55

* : Continuous variables shown as mean (SD)

[P] : p-value for test comparing patients of surgeons performing < 21 resections to those of surgeons performing ≥ 21 resections

Table 5.7 Operative variables according to total number of resections by the surgeon during the study period

	< 21 resections (n=323)		≥ 21 resections (n=360)		p value [P]
Operative time (min.)	174	(52)*	140	(44)*	<0.001
Estimated blood loss (ml)	971	(784)*	702	(528)*	<0.001
Perioperative transfusion	232	(71.8%)	209	(58.1%)	<0.001
Intraoperative tumour spill	46	(14.2%)	446	(12.8%)	0.58
Inadvertent rectal perforation	44	(13.6%)	41	(11.4%)	0.38
Operative procedure					0.007
LAR	164	(50.8%)	220	(61.1%)	
APR	159	(49.2%)	140	(38.9%)	
If LAR - stapled anastomosis	95	(57.9%)	125	(56.8%)	0.83
If APR - two-teamed	102	(64.2%)	103	(73.6%)	0.08

* : Continuous variables shown as mean (SD)

[P] : p-value for test comparing patients of surgeons performing < 21 resections to those of surgeons performing ≥ 21 resections

Table 5.8 Tumour characteristic and use of adjuvant therapy according to total number of resections by the surgeon during the study period

	< 21 resections (n=323)		≥ 21 resections (n=360)		p value [P]
Stage					0.65
1	71	(22.0%)	69	(19.2%)	
2	128	(39.6%)	158	(43.9%)	
3	122	(37.8%)	130	(36.1%)	
4 [S]	2	(0.6%)	3	(0.8%)	
Grade					0.56
well differentiated	25	(7.7%)	32	(8.9%)	
moderately differentiated	257	(79.6%)	291	(80.8%)	
poorly differentiated	41	(12.7%)	37	(10.3%)	
Distal margin < 2 cm	61	(18.9%)	49	(13.6%)	0.06
Radial margin status unknown	10	(3.1%)	9	(2.5%)	0.82
Vascular/neural invasion	50	(15.5%)	58	(16.1%)	0.82
Signet ring or mucinous	46	(14.2%)	39	(10.8%)	0.18
Size (cm)	4.3	(1.8)*	4.4	(1.9)*	0.27
Adjuvant therapy used	121	(38.3%) [a]	116	(32.9%) [b]	0.14

* : Continuous variables shown as mean (SD)

[P] : p-value for test comparing patients of surgeons performing < 21 resections to those of surgeons performing ≥ 21 resections

[S] : Synchronous liver resection for metastatic disease

[a] : n=326 (perioperative mortality cases excluded)

[b] : n=352 (perioperative mortality cases excluded)

Table 5.9 Univariate comparisons of disease specific survival (DSS) and local recurrence (LR) rates according to various demographic and preoperative factors

Factor (n)	DSS (%)	p value ^{P}	LR (%)	p value ^{P}
Demographic				
Gender		0.16		0.63
female (264)	50.1		35.6	
male (419)	44.0		32.4	
Age, years		0.03		0.17
< 40 (15)	57.8		25.7	
40-59 (202)	49.7		30.0	
60-79 (293)	45.7		33.9	
≥ 80 (93)	33.5		43.5	
Preoperative				
Obstruction		0.02		0.03
Yes (40)	15.1		54.2	
No (643)	48.1		32.3	
Fixation		0.12		0.27
Yes (50)	28.9		42.8	
No (633)	47.6		35.1	
Goldman Class		0.004		0.04
1 (411)	48.6		31.4	
2 (206)	40.0		40.0	
3 (66)	47.3		25.0	
Level		0.03		0.32
low (168)	33.6		39.7	
mid (266)	47.7		31.8	
high (249)	53.6		31.8	
CEA, mg/dl ^{N}		<0.001		0.001
< 5.0 (248)	57.6		24.7	
≥ 5.0 (161)	39.3		37.8	

^{N} : n = 409

^{P} : Log Rank p value

DSS : Disease-specific survival

LR : Local recurrence

Table 5.10 Univariate comparisons of disease-specific survival (DSS) and local recurrence (LR) rates according to various operative factors

Factor (n)	DSS (%)	p value [P]	LR (%)	p value [P]
Colorectal-trained surgeon		0.009		<0.001
Yes (109)	60.8		13.4	
No (574)	43.8		37.4	
Total number resections by surgeon		0.001		<0.001
< 21 (323)	38.8		42.2	
≥ 21 (360)	53.5		26.0	
Operative time, min.		0.47		0.35
0-114 (144)	47.1		36.4	
115-149 (179)	49.4		28.6	
150-184 (186)	47.8		32.5	
≥ 185 (174)	41.2		38.2	
Estimated blood loss, ml		0.004		0.08
0-499 (149)	49.7		30.0	
500-699 (178)	57.1		28.0	
700-999 (137)	40.0		33.4	
≥ 1000 (219)	39.2		40.6	
Perioperative transfusion		<0.001		0.007
Yes (441)	40.2		39.7	
No (242)	58.0		26.6	
ITS or IPR		<0.001		<0.001
Yes (99)	25.3		60.0	
No (584)	50.0		29.0	
Operative procedure		0.16		0.79
LAR (384)	51.1		32.6	
APR (299)	40.1		35.2	
Enbloc resection		0.01		0.04
Yes (49)	34.1		32.7	
No (624)	47.3		48.1	

[P] : Log Rank p value   ITS : intraoperative tumour spill   IPR : inadvertent rectal perforation

Table 5.11 Disease-specific survival (A) and local recurrence (B) rates according to surgeon-related factors.

A: Disease-Specific Survival

	≥ 21 resections (n=360)	< 21 resections (n=323)
Colorectal-trained (n=109)	67.3%	54.5%
Non-colorectal-trained (n=574)	49.0%	39.2%

p = 0.01 (Logrank)

B: Local Recurrence

	≥ 21 resections (n=360)	< 21 resections (n=323)
Colorectal-trained (n=109)	10.4%	21.1%
Non-colorectal-trained (n=574)	27.8%	44.6%

p = 0.005 (Logrank)

Figure 5.1. Kaplan-Meier curves of disease-specific survival by presence of colorectal-trained surgeon

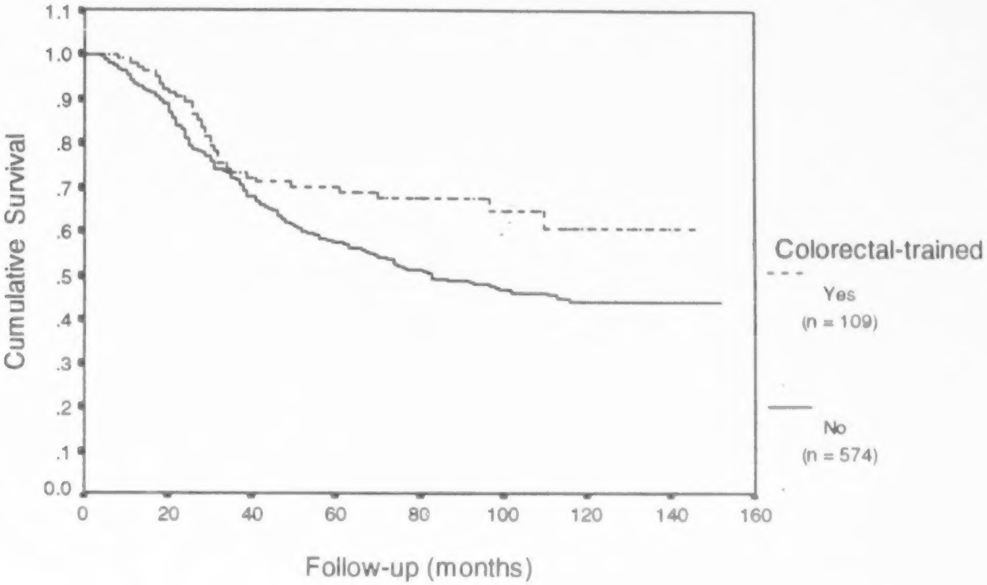


Figure 5.2 Kaplan-Meier curves for disease-specific survival by number of rectal cancer resections performed by the surgeon.

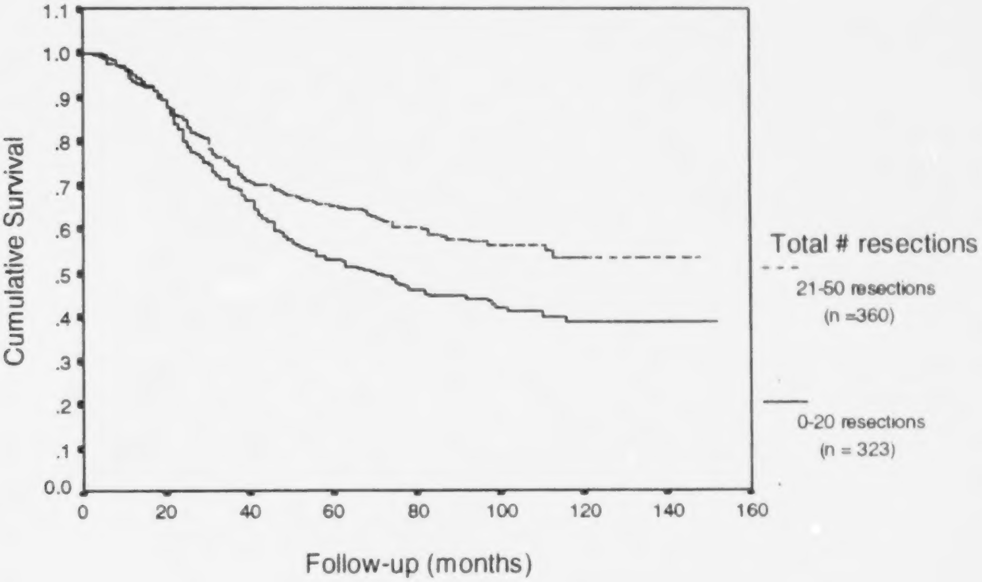


Figure 5.3 Kaplan-Meier curves for disease-specific survival by number of rectal cancer resections and/or surgical training.

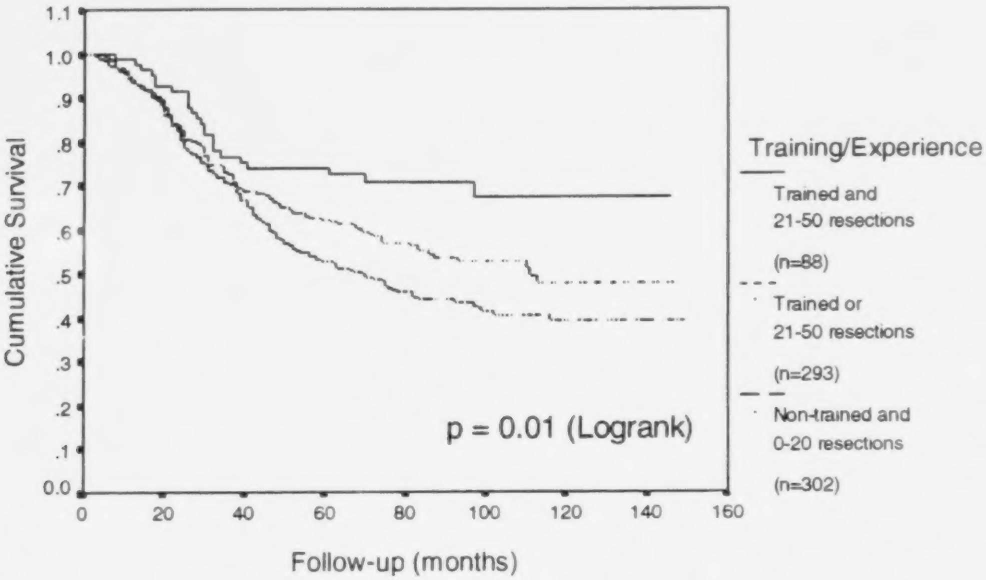


Figure 5.4 Kaplan-Meier curves for local recurrence by presence of colorectal-trained surgeon

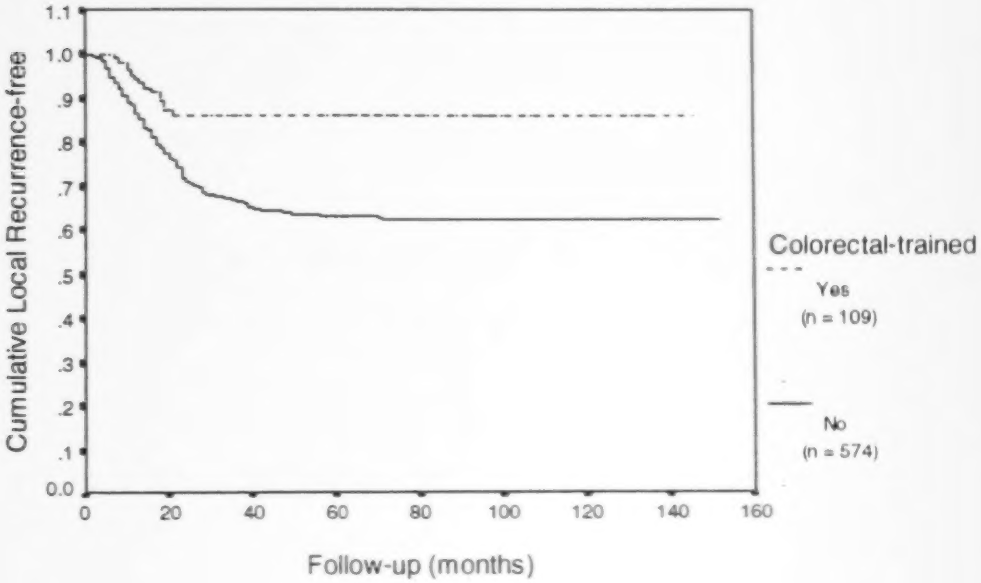


Figure 5.5 Kaplan-Meier curves for local recurrence by number of rectal cancer resections performed by the surgeon

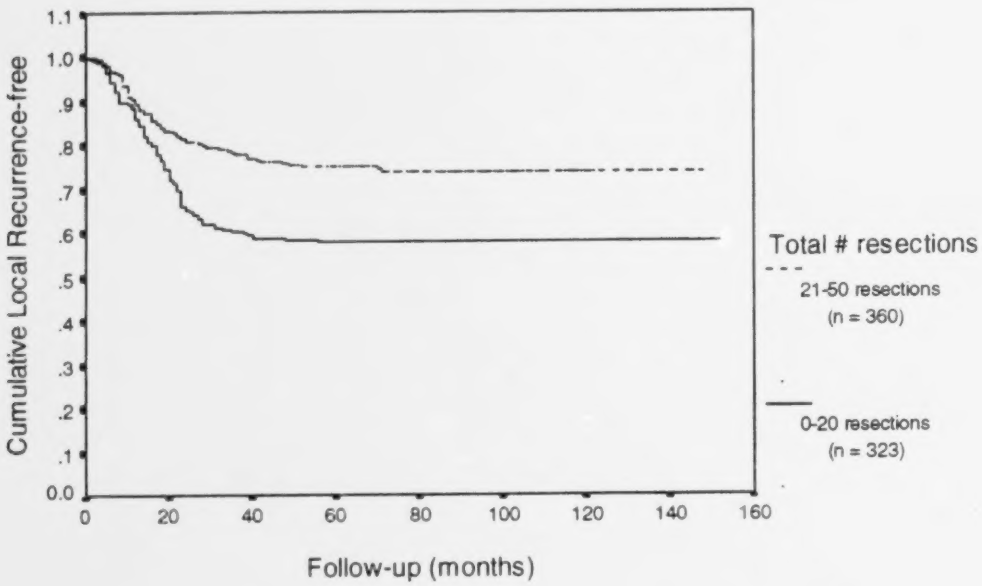


Table 5.12 Univariate comparisons of disease-specific survival (DSS) and local recurrence (LR) rates according to various tumour factors

Factor (n)	DSS (%)	p value [P]	LR (%)	p value [P]
Stage		<0.001		<0.001
1 (140)	80.7		13.5	
2 (286)	48.0		32.5	
3 and 4 [S] (257)	26.1		46.7	
Differentiation (grade)		<0.001		0.002
well (57)	66.1		22.2	
moderate (548)	46.9		34.1	
poor (78)	29.8		46.5	
Distal margin ≥ 2 cm		0.58		0.04
Yes (573)	48.2		32.7	
No (110)	49.1		41.7	
Radial margin status		0.06		0.004
Clear (664)	47.1		32.7	
Unknown (19)	16.9		71.0	
Vascular/neural invasion		<0.001		<0.001
Yes (108)	18.7		51.5	
No (575)	51.8		30.6	
Type		0.002		<0.001
Adenocarcinoma (598)	47.1		32.2	
Mucinous (75)	44.4		39.0	
Signet ring (7)	17.8		81.0	
Other (3)	0		100	
Size, cm		0.26		0.27
< 5 (373)	47.7		31.3	
≥ 5 (310)	44.9		36.5	

[P] : Log Rank p value [S] : synchronous liver resection for metastatic disease

Table 5.13 Univariate comparisons of disease-specific survival (DSS) and local recurrence (LR) according to three classifications of adjuvant therapy

	DSS (%)	p value [P]	LR (%)	p value [P]
Classification 1 [N]		<0.001		0.02
None (432)	51.7		32.8	
Preop RT (50)	43.5		20.0	
Preop RT + chemo (18)	35.4		11.8	
Postop RT (143)	31.7		43.6	
Postop RT + chemo (26)	39.3		37.3	
Classification 2 [N]		<0.001		0.66
None (432)	51.7		32.8	
Present (237)	36.1		35.5	
Classification 3 [N]		<0.001		0.004
None (432)	51.7		32.8	
Preoperative (68)	47.4		18.0	
Postoperative (169)	32.1		42.8	

[N] : n = 669 (perioperative mortality excluded) [P] : Log Rank p value

RT : radiotherapy Chemo : chemotherapy

Table 5.14 Univariate comparisons of perioperative mortality according to various demographic and preoperative variables (n = 683).

Factor (n)	Perioperative mortality, n (%)		p value [p]
Demographic			
Gender			0.82
female (264)	5	(1.9)	
male (419)	9	(2.1)	
Age, years			<0.001
< 40 (15)	0		
40-59 (202)	0		
60-79 (393)	7	(1.8)	
≥ 80 (73)	7	(9.6)	
Preoperative			
Obstruction			0.17
Yes (40)	2	(5.0)	
No (643)	12	(1.9)	
Fixation			0.31
Yes (50)	12	(1.9)	
No (633)	2	(4.0)	
Goldman Class			<0.001
1 (411)	2	(0.5)	
2 (206)	6	(2.9)	
3 (66)	6	(9.1)	
Level			0.14
low (168)	4	(2.4)	
mid (266)	2	(0.8)	
high (249)	8	(3.2)	

[p] : chi-square or Fisher exact p value

Table 5.15 Univariate comparisons of perioperative mortality according to various operative variables.

Factor (n)	Perioperative mortality, n (%)		p value [P]
Colorectal-trained surgeon			0.36
Yes (109)	1	(0.9)	
No (574)	13	(2.3)	
Total number resections by surgeon			0.83
≥ 21 (360)	7	(1.9)	
< 21 (323)	7	(2.2)	
Operative time, min.			0.51
0-114 (144)	5	(3.5)	
115-149 (179)	2	(1.1)	
150-184 (186)	4	(2.2)	
≥ 185 (174)	3	(1.7)	
Estimated blood loss, ml			0.61
0-499 (149)	4	(2.7)	
500-699 (178)	2	(1.1)	
700-999 (137)	2	(1.5)	
≥ 1000 (219)	6	(2.7)	
Perioperative transfusion			0.09
Yes (441)	12	(2.7)	
No (242)	2	(0.8)	
ITS or IPR			0.13
Yes (99)	4	(4.0)	
No (584)	10	(1.7)	
Operative procedure			0.94
LAR (384)	6	(2.0)	
APR (299)	8	(2.1)	

[P] : chi-square or Fisher exact p value   ITS: intraoperative tumour spill   IPR: inadvertent rectal perforation

Table 5.16 Univariate comparisons of generic complications according to various demographic and preoperative variables.

Factor (n)	≥ 1 generic complication, %	p value [P]
Demographic		
Gender		0.92
female (259)	26.3	
male (410)	26.6	
Age, years		0.04
< 40 (15)	6.7	
40-59 (202)	22.3	
60-79 (386)	27.7	
≥ 80 (66)	36.4	
Preoperative		
Obstruction		0.26
Yes (40)	34.2	
No (643)	27.0	
Fixation		0.14
Yes (38)	35.4	
No (631)	25.8	
Goldman Class		0.52
1 (409)	24.9	
2 (200)	28.5	
3 (60)	30.0	
Level		0.006
low (164)	36.0	
mid (264)	24.2	
high (241)	22.4	

[P] : chi-square or Fisher exact p value

Table 5.17 Univariate comparisons of generic complications according to various operative variables (n=669).

Factor (n)	≥ 1 generic complication, %	p value ^{P}
Colorectal-trained surgeon		0.006
Yes (108)	15.7	
No (561)	28.5	
Total number resections by surgeon		0.10
≥ 21 (353)	23.8	
< 21 (316)	29.4	
Operative time, min.		0.07
0-114 (139)	22.3	
115-149 (177)	21.5	
150-184 (182)	29.1	
≥ 185 (171)	32.1	
Estimated blood loss, ml		<0.001
0-399 (145)	20.0	
400-699 (176)	18.2	
700-999 (135)	31.1	
≥ 1000 (213)	34.7	
Perioperative transfusion		<0.001
Yes (429)	15.4	
No (240)	32.6	
ITS or IPR		0.30
Yes (95)	22.1	
No (574)	27.2	
Operative procedure		0.001
LAR (376)	21.5	
APR (293)	32.8	

^{P} : chi-square p value

ITS : intraoperative tumour spill IPR : inadvertent rectal perforation

Table 5.18 Univariate comparisons of LAR-specific complications according to various demographic and preoperative variables (n = 332)

Factor (n)	≥ 1 LAR complication, %	p value [P]
Demographic		
Gender		0.05
female (149)	11.4	
male (183)	19.1	
Age, years		0.67
< 40 (7)	28.6	
40-59 (93)	15.1	
60-79 (197)	14.7	
≥ 80 (35)	20.0	
Preoperative		
Obstruction		0.37
Yes (30)	10.0	
No (302)	16.2	
Fixation		0.36
Yes (12)	25.0	
No (320)	15.3	
Goldman Class		0.82
1 (189)	16.4	
2 (110)	15.5	
3 (33)	12.1	
Level		0.27
low (1)	0	
mid (121)	19.8	
high (210)	13.3	

[P] : chi-square or Fisher exact p value

Table 5.19 Univariate comparisons of LAR-specific complications according to various operative variables. (n = 332)

Factor (n)	≥ 1 LAR complication, %	p value [P]
Colorectal-trained surgeon		0.91
Yes (72)	15.8	
No (260)	15.3	
Total number resections by surgeon		0.01
≥ 21 (192)	11.5	
< 21 (140)	21.4	
Operative time, min.		0.13
0-114 (89)	11.2	
115-149 (89)	13.5	
150-184 (79)	15.2	
≥ 185 (75)	24.0	
Estimated blood loss, ml		0.67
0-399 (118)	13.6	
500-699 (108)	14.8	
700-999 (53)	20.8	
≥ 1000 (53)	17.0	
Perioperative transfusion		0.70
Yes (157)	16.6	
No (175)	14.9	
ITS or IPR		0.37
Yes (30)	10.0	
No (302)	16.2	
Anastomosis		0.21
Stapled (191)	17.8	
Handsewn (141)	12.8	
Protective ostomy used		0.35
Yes (38)	10.5	
No (294)	16.3	

[P] : chi-square or Fisher exact p value ITS: intraoperative tumour spill IPR: inadvertent rectal perforation

Table 5.20 Univariate comparisons of APR-specific complications according to various demographic and preoperative variables. (n = 261)

Factor (n)	≥ 1 APR complication, %	p value [p]
Demographic		
Gender		0.43
female (86)	36.1	
male (175)	41.1	
Age, years		0.57
< 40 (8)	62.5	
40-59 (89)	37.1	
60-79 (149)	40.0	
≥ 80 (15)	40.0	
Preoperative		
Obstruction		0.98
Yes (5)	40.0	
No (256)	39.5	
Fixation		0.31
Yes (32)	31.3	
No (229)	40.6	
Goldman Class		0.67
1 (176)	40.9	
2 (66)	34.8	
3 (19)	42.1	
Level		0.30
low (145)	35.9	
mid (113)	43.4	
high (3)	66.7	

[p] : chi-square or Fisher exact p value

Table 5.21 Univariate comparisons of APR-specific complications according to various operative variables. (n = 261)

Factor (n)	≥ 1 APR complication, %	p value [P]
Colorectal-trained surgeon		0.005
Yes (27)	14.8	
No (234)	42.3	
Total number resections by surgeon		<0.001
≥ 21 (131)	28.2	
< 21 (130)	50.8	
Operative time, min.		0.80
0-114 (41)	36.6	
115-149 (63)	36.5	
150-184 (80)	43.8	
≥ 185 (77)	39.0	
Estimated blood loss, ml		0.13
0-399 (18)	16.7	
400-699 (48)	39.6	
700-999 (62)	35.5	
≥ 1000 (133)	44.4	
Perioperative transfusion		0.05
Yes (213)	42.3	
No (48)	27.1	
ITS or IPR		0.007
Yes (54)	55.5	
No (207)	32.3	
Primary perineal closure		0.02
Yes (167)	34.1	
No (94)	49.0	
Two-teamed approach		0.30
Yes (183)	41.5	
No (234)	34.6	

[P] : chi-square or Fisher exact p value ITS: intraoperative tumour spill IPR: inadvertent rectal perforation

Table 5.22 Univariate comparisons of length of hospital stay (LOS) according to various demographic and preoperative variables (n = 683).

Factor (n)	**Mean LOS, days (SD)**		**p value ^{p}**
Demographic			
Gender			0.69
female (264)	15.3	(9.3)	
male (419)	15.6	(9.8)	
Age, years			<0.001
< 40 (15)	11.7	(4.1)	
40-59 (202)	13.5	(7.7)	
60-79 (393)	15.3	(8.2)	
≥ 80 (73)	22.5	(16.6)	
Preoperative			
Obstruction			0.82
Yes (40)	15.8	(12.1)	
No (643)	15.4	(9.4)	
Fixation			0.02
Yes (50)	18.4	(11.8)	
No (633)	15.2	(9.4)	
Goldman Class			<0.001
1 (411)	13.9	(7.6)	
2 (206)	17.2	(11.1)	
3 (66)	19.9	(12.9)	
Level			<0.001
low (168)	18.8	(11.0)	
mid (266)	15.3	(9.4)	
high (249)	13.3	(8.2)	

p : *t* test or ANOVA p value

Table 5.23 Univariate comparisons of length of hospital stay (LOS) according to various operative variables. (n = 683)

Factor (n)	Mean LOS, days (SD)	p value ^{p}
Colorectal-trained surgeon		0.006
Yes (109)	13.2 (7.0)	
No (574)	15.9 (10.0)	
Total number resections by surgeon		0.03
≥ 21 (360)	14.7 (9.8)	
< 21 (323)	16.3 (9.4)	
Operative time, min.		0.02
0-114 (144)	13.5 (9.0)	
115-149 (179)	15.2 (10.5)	
150-184 (186)	16.4 (9.4)	
≥ 185 (174)	16.4 (9.2)	
Estimated blood loss, ml		<0.001
0-399 (149)	12.2 (5.9)	
400-699 (178)	13.4 (6.6)	
700-999 (137)	17.8 (13.1)	
≥ 1000 (219)	17.9 (10.1)	
Perioperative transfusion		<0.001
Yes (441)	17.6 (10.7)	
No (242)	11.6 (5.4)	
ITS or IPR		0.003
Yes (99)	18.2 (13.7)	
No (584)	15.0 (8.6)	
Operative procedure		<0.001
LAR (384)	13.3 (8.5)	
APR (299)	18.2 (10.2)	
Enbloc resection		0.84
Yes (49)	15.7 (9.0)	
No (634)	15.4 (9.7)	

p : *t* test or ANOVA p value   ITS - intraoperative tumour spill   IPR - inadvertent rectal perforation

Table 5.24 Association between generic complications and length of stay

	Mean LOS, days (SD)	p value [p]
Generic Complications		<0.001
No generic complications (492)	13.3 (6.6)	
≥ 1 generic complication (177)	21.5 (13.1)	

p : *t* test p value

Chapter 6

Results: Multivariate analysis

The purpose of these analyses was to examine predictors of various outcomes in a multivariate model. The intention was not to construct a predictive model, but rather to examine potential predictors while controlling for confounding and interaction. Survival, local recurrence, perioperative mortality, and postoperative morbidity outcomes are examined in this fashion.

6.1 Disease-Specific Survival

As previously described, disease-specific survival included only deaths from rectal cancer and was treated as a dichotomous variable. Cox proportional hazard regression analysis was performed by a forward stepwise approach examining all variables assessed by univariate analysis (Tables 5.9, 5.10, 5.12, 5.13) except preoperative CEA which was missing in 274 patients and thus excluded because of unacceptable loss of effective regression sample size. Criteria for insertion into the model was $p < 0.10$ of the likelihood ratio statistic so as to reduce the possibility of a variable of borderline significance being excluded from the final model. Adjuvant therapy was recoded to a three-level variable as per Classification 3 in Table 5.13:

- no adjuvant therapy
- preoperative adjuvant therapy
- postoperative adjuvant therapy

Tumour type was converted to a binary variable, for reasons of too few cases in some cells:

- Adenocarcinoma
- Mucinous, signet ring and other

All possible two-way interaction terms were assessed during the stepwise regression. All three-way interaction terms involving colorectal training and stage, or number of resection by the surgeon and stage because of the clinical importance of these variables. None of the interaction terms examined had a p-value < 0.10.

Each variable was first examined by Cox regression as a main effect, that is with no other variables in the model. Without exception, resultant p values from these analyses were very similar to those obtained by the previous log rank test. Based on widespread acceptance of stage as a prognostic factor for disease-specific survival, model building began with this variable.

Regardless of other variables in the model, colorectal-training and number of resections by the surgeon were statistically significant as main effects in their association with disease-specific survival, supporting the hypothesis that both of these factors were important independent predictors of disease-specific survival.

It was noteworthy that when examined in separate models with stage, the statistical significance of obstruction, estimated blood loss, perioperative transfusion, and enbloc resection observed on univariate analysis was no longer present. This suggested that these variables were highly associated with stage and were not predictors for disease-specific survival independent of stage. In a similar fashion, the type of tumour was not a statistically significant predictor for disease-specific survival when examined in a model containing grade. This was not unexpected as it is known that mucinous and signet ring tumours are characteristically of high grade (poorly differentiated).

Although both age and Goldman Class were associated with disease-specific survival on univariate analysis, only age was significant when both variables were examined together in a model. This is explained again by the high correlation between age and Goldman Class, with age being a component of Goldman Class. As Goldman Class was designed as a measure of perioperative mortality risk and not a measure of long-term cancer survival, age was preferentially retained in the final model.

The absence of a statistical association with disease-specific survival on univariate analysis was confirmed on multivariate analysis for all such variables. Otherwise stated, no variable was found to be statistically significant on multivariate analysis that was not previously found to be statistically significant on univariate analysis.

The univariate examination of adjuvant therapy with disease-specific survival suggested that the use of preoperative adjuvant therapy, and particularly postoperative adjuvant therapy, were actually associated with decreased disease-specific survival. When this three-level variable was examined in a Cox regression model with stage, this relationship no longer existed. This finding supports the conclusion that patient selection for adjuvant therapy was responsible for the univariate association with reduced disease-specific survival, with generally only advanced stage patients being offered adjuvant therapy.

The final Cox proportional hazard regression model for the outcome of disease specific death is shown in Table 6.1. Colorectal training, number of resections performed by the surgeon, stage, grade, vascular or lymphatic invasion, tumour spill or inadvertent rectal perforation, and age were found to be independent prognostic factors for disease-specific survival. Adjuvant therapy was not significant when considered as a dichotomous (any adjuvant therapy vs. none) or categorical (none, preoperative or postoperative) variable, with p values of 0.88 and 0.98 respectively. The detrimental impact of grade on disease-specific survival appears to be largely attributable to poorly differentiated tumours (grade 3). When grade was then made dichotomous (well or moderately differentiated vs. poorly differentiated), minimal changes were found in the risk estimations of the model.

Hazards ratios presented in Table 6.1 are estimations of relative risk. It is instructive to compare these estimations to estimated relative risks obtained from univariate analysis. For example, from Table 5.10, the disease-specific survival rate was 60.8% among patients of colorectal-trained surgeons and 43.8% in patients of non-colorectal-trained surgeons. Thus, the relative risk for disease-specific death could be estimated by:

$[1-0.438]/[1-0.608] = 1.43$

This estimated relative risk of 1.43 is similar to the hazard ratio of 1.52 from the final Cox proportional hazard model of Table 6.1. This suggests that control of other prognostic factors did not change the univariate risk of colorectal surgical training appreciably. Similar calculations and comparisons were made of other factors both included and not included in the final model, again which showed minimal differences in the univariate and multivariate risk estimations (Table 6.2).

6.2 Local Recurrence

Local recurrence was defined by any anastomotic, pelvic, or perineal tumour confirmed histologically or by CT scan prior to death. Thus, this was a dichotomous outcome.

A similar approach was taken to Cox proportional hazards regression as was outlined in the previous section. Again, no statistically significant interaction terms were identified.

Regardless of other variables in the model, colorectal surgical training and number of resections by the surgeon were statistically significant in their association with local recurrence, which supports the hypothesis that both of these factors were independent predictors of local recurrence.

Similar findings found with disease-specific survival were observed in examining local recurrence on a multivariate level with respect to the effect of obstruction, estimated blood loss, perioperative transfusion, and enbloc resection. However, both grade and tumour type were no longer significantly associated with local recurrence when stage was included in the Cox regression model. This somewhat unexpected finding suggests that advanced grade may be more a measure of a tumour's propensity for distant metastases than for its local aggressiveness.

Again, the absence of a statistical association with local recurrence on univariate analysis was confirmed on multivariate analysis for all such variables.

In contrast with the analysis of disease-specific survival, adjuvant therapy was a significant prognostic factor for local recurrence after controlling for other factors. An overall protective effect of adjuvant therapy was observed with the greatest apparent benefit when adjuvant therapy was given preoperatively. This was likely the result of the radiotherapy and has been confirmed in previously mentioned clinical trials.

The final regression model is shown in Table 6.3. The presence of a non-colorectal-trained surgeon, the presence of a surgeon performing < 21 resections, inadvertent rectal perforation/inadvertent tumour spill, vascular/lymphatic invasion, and advanced stage were found to be significant independent prognostic factors for local recurrence. Absence of adjuvant therapy was associated with local recurrence with preoperative adjuvant therapy having a significant protective effect.

Comparison of the univariate and multivariate risk estimations of these factors in the final model for local recurrence was performed as described in the previous section (Table 6.4). Minimal differences were noted, with the exception of adjuvant therapy. The calculated univariate relative risks for local recurrence with preoperative adjuvant therapy and postoperative adjuvant therapy were 0.55 and 1.30 respectively, in contrast to the hazard ratios of 0.33 and 0.79 respectively from the final Cox regression model. As predominantly advanced stage patients received adjuvant therapy, control of stage in the multivariate analysis was crucial to the assessment of the effect of adjuvant therapy on local recurrence.

6.3 Perioperative Mortality

Forward stepwise logistic regression was applied to this dichotomous outcome in which perioperative mortality was considered absent or present. Logistic regression was appropriate as no censoring was observed for this outcome.

Variables assessed included those presented in the univariate analysis (Tables 5.14 and 5.15). Inclusion in the model required significance of $p < 0.10$ of the likelihood ratio statistic. All possible two-way interactions were tested and none were found to be significant.

On univariate analysis, both age and Goldman Class were found to be associated with perioperative mortality. As stated in the univariate analysis of perioperative mortality, there was significant correlation between age and Goldman Class, largely a result of age being an integral component of the Goldman Class. Thus, when both were entered in the regression model, only Goldman Class was found to be significant whereas the p value for the coefficient of age was 0.11. The inclusion or exclusion of age from the model resulted in minimal change in the Goldman Class coefficients.

No other factors were found to approach statistical significance in the modeling procedure. Thus, the final model contained only Goldman Class as a significant prognostic factor for perioperative mortality (Table 6.5). Specifically, neither colorectal training nor number of resections by the surgeon were statistically significant risk factors for perioperative mortality. When both of these variables were added to the model presented in Table 6.2, their respective p values were 0.28 and 0.83. However, as similarly noted on univariate analysis, the power to detect the trend toward decreased perioperative mortality in patients of colorectal-trained surgeons was calculated at only 39%.

6.4 Complications - Generic, LAR-Specific and APR-Specific

A similar logistic regression approach was undertaken with the separate outcomes of generic, LAR-specific, and APR-specific complications. Separate models were created for each dichotomous outcome. Outcomes were coded as (i) no complications or (ii) ≥ 1 complication.

Variables tested in the univariate analyses (Table 5.16 - 5.21) as well as stage and grade were assessed for each respective outcome.

The resultant final model for the outcome of generic complications, which included advancing age, perioperative transfusion and non-colorectal-trained surgeons as independent prognostic factors, is shown in Table 6.6. It is noteworthy that the number of resections by the surgeon was not significant in the model. No significant interaction terms were found. This model suggested that generic complications were dependent upon both a baseline patient risk (as measured by age) and operative factors (colorectal-training, blood transfusion).

Table 6.7 shows the regression analysis for the outcome of LAR-specific complications. Three separate outcomes are examined in separate models: (1) LAR-specific complications (none/≥1 complication), (2) anastomotic leak (absent/present), and (3) anastomotic stricture (absent/present). These models include all patients undergoing LAR who did not suffer perioperative mortality. When anastomotic stricture and leak are examined as a combined variable (LAR-specific complication), the number of resections performed by the surgeon was the only significant prognostic factor.

Male sex and absence of a stapled anastomosis (i.e. presence of a handsewn anastomosis) were significant independent prognostic factors for the occurrence of an anastomotic leak (Table 6.7). As previously hypothesized, the narrow male pelvis likely accounted for this observation.

In terms of anastomotic stricture, <21 resections by the surgeon and the use of a stapled anastomosis were significant prognostic factors (Table 6.7). This suggests that although stapled anastomoses appeared superior to the handsewn technique in terms of postoperative leak risk, anastomotic strictures were more common following stapled anastomoses. Previous publications support this finding.[35]

No significant interaction terms were found in any of these models.

Finally, the multivariate model for APR-specific complications is seen in Table 6.8. The presence of a surgeon performing < 21 resections, intraoperative tumour spill/inadvertent rectal perforation, and the absence of a primary perineal closure were significant risk factors for ≥ 1 APR-specific complication. If number of resections by the surgeon was excluded from the model, colorectal-training became a significant factor suggesting that surgeon-related factors certainly played a role in the development of these complications.

In addition, significant interaction was noted between intraoperative tumour spill/inadvertent rectal perforation and closure of the perineal wound. As a result of the interaction, the odds ratios presented for each of these variables in Table 6.8 are meaningful only when the other variable is in the baseline category. For example, the odds ratio of 13.0 for APR-specific complications with intraoperative tumour spill/inadvertent perforation is interpretable only in the absence of a primary perineal closure. The effects of this interaction are further detailed in Table 6.9. Adjusted odds ratios and their confidence intervals were calculated using a variance-covariance matrix approach,[154] with the absence of both variables defined to have an odds ratio of 1.0. Thus, the odds ratios 13.0 and 0.73 are simply calculated as e^B for each variable. When intraoperative tumour spill/inadvertent rectal perforation occurred and a primary perineal closure was performed, the odds ratio for APR-specific complications was 1.09. This was calculated by adding the coefficients (Beta) from Table 6.8 for intraoperative tumour spill/inadvertent rectal perforation, primary perineal closure, and the interaction term, and then computing the exponent:

$$\text{OR (both variables present)} = \exp(-0.31+2.57-2.17) = 1.09$$

Simply stated, these results suggest that the risk of $\geq$ APR-specific complications following intraoperative tumour spill/inadvertent rectal perforation is massively increased (OR=13.0) when the perineum is not closed primarily. Similarly, the apparent protective effect of a primary perineal closure is increased if intraoperative tumour spill/inadvertent rectal perforation did not occur (OR=0.73). When both primary perineal closure and tumour spill/rectal perforation take place, the net effect (OR=1.09) is close to the baseline (OR=1.0). Clinically, this suggests that if inadvertent tumour spill/rectal perforation has been identified intraoperatively, primary closure of the perineal wound is important for reducing postoperative APR-specific complications.

6.5 Length of Stay

The continuous variable of length of stay in hospital after operation was noted to be appreciably positively skewed. Thus, for the purposes of multiple linear regression, the natural logarithm of this continuous outcome was treated as the dependent variable in the regression equation. The results of this stepwise regression showed increased age, increased Goldman

Class, APR, perioperative transfusion, and earlier year of operation to be independently associated with prolonged length of stay (Table 6.10).

APR is a somewhat larger operation than LAR in that two separate incisions are used, a colostomy is fashioned, and the perineal wound is often very painful in the immediate postoperative period. Thus, it was not surprising to find APR independently associated with length of stay. The association of length of stay with colorectal training and number of resections by the surgeon identified on univariate analysis was not found on multivariate analysis (p values 0.12 and 0.13 respectively). This may be explained by the preferential use of LAR among both colorectal-trained surgeons and surgeons performing ≥ 21 resections over the study period.

A progressive decline in mean length of stay was noted from 1983 (17.4 days) to 1990 (12.7 days). This was likely reflective of the changes in practice patterns over the 8-year study period.

The occurrence of complications was not entered into this regression model as the temporal sequence could not be established in every case. Alternatively stated, did prolonged length of stay follow the occurrence of a complication, or was the complication caused by a prolonged length of stay? Instead, the linear regression model building process was repeated excluding all cases with complications. The resultant model included the same variables found for the analysis of all patients, with the exception of age (p=0.09). This suggests that year of operation, Goldman Class, procedure type and use of blood transfusions are prognostic factors for length of stay regardless of presence of complications.

Table 6.1 Cox proportional hazard regression model using disease-specific mortality as the outcome variable

	B	SE(B)	HR	95% CI	p value
Non-colorectal-trained surgeon	0.42	0.19	1.52	1.05-2.20	0.03
< 21 resections by surgeon	0.33	0.12	1.40	1.11-1.77	0.005
Rectal perforation or tumour spill	0.70	0.14	2.01	1.52-2.67	<0.001
Vascular or lymphatic invasion	0.56	0.14	1.75	1.33-2.29	0.001
Grade*					0.02^P
2	0.07	0.27	1.07	0.63-1.83	0.80
3	0.51	0.30	1.66	0.92-3.00	0.09
Stage **					$<0.001^P$
2	1.01	0.24	2.74	1.72-4.36	<0.001
3	1.74	0.23	5.71	3.62-9.01	<0.001
Age***					0.02^P
40-59	0.27	0.43	1.31	0.57-3.03	0.53
60-79	0.65	0.42	1.91	0.84-4.35	0.12
≥80	0.52	0.45	1.67	0.70-4.06	0.25

B: coefficient; SE(B): standard error of coefficient

HR: hazard ratio; CI: confidence bounds for hazard ratio

*: comparison group is grade = 1

**: comparison group is stage = 1

***: comparison group is age < 40 years

^{P}: overall p-value

Table 6.2 Comparison of univariate relative risks (RRu), hazard ratios from main effects Cox regression model (HRm), and hazard ratios from final Cox regression model (HRf) for disease-specific mortality

Variables	RRu	HRm	HRf
In Final Cox Model			
Non-colorectal-trained surgeon	1.43	1.60	1.52
< 21 resections by surgeon	1.31	1.43	1.40
Rectal perforation or tumour spill	1.59	1.93	2.01
Vascular or lymphatic invasion	1.68	1.87	1.75
Grade*			
2	1.46	1.32	1.07
3	2.07	1.72	1.66
**Stage ** **			
2	2.69	3.11	2.74
3	3.82	6.30	5.71
Age***			
40-59	1.19	1.08	1.31
60-79	1.28	1.37	1.91
≥80	2.06	1.63	1.67
Not in final Cox model			
Male gender	1.14	1.18	-
Obstruction	1.64	1.87	-
Fixation	1.63	1.36	-
Margin < 2 cm	0.98	1.19	-
Abdominoperineal resection ****	1.22	1.17	-
Adjuvant therapy^{A}	1.09	1.00	-
preop	1.4	1.73	-
postop			-

^{A}: comparison group is no adjuvant therapy

*: comparison group is grade = 1

**: comparison group is stage = 1

***: comparison group is age < 40 years

****: comparison group is low anterior resection

Table 6.3 Cox proportional hazard regression model using local recurrence as the outcome variable

	B	SE(B)	HR	95% CI	p value
Non-colorectal-trained surgeon	0.91	0.28	2.49	1.43-4.33	0.001
< 21 resections by surgeon	0.59	0.15	1.80	1.35-2.40	<0.001
Rectal perforation or tumour spill	1.05	0.16	2.86	2.09-3.91	<0.001
Vascular or lymphatic invasion	0.52	0.17	1.69	1.20-2.36	0.002
Adjuvant therapy *					0.002 ^{P}
preop	-1.10	0.32	0.33	0.18-0.62	0.001
postop	-0.24	0.16	0.79	0.57-1.09	0.15
Stage **					<0.001 ^{P}
2	1.01	0.27	2.74	1.62-4.64	<0.001
3	1.53	0.27	4.62	2.71-7.89	<0.001

B: coefficient; SE(B): standard error of coefficient

HR: hazard ratio; CI: confidence bounds for hazard ratio

*: comparison group is no adjuvant therapy

**: comparison group is stage = 1

^{P}: overall p-value

Table 6.4 Comparison of univariate relative risks (RRu), hazard ratios from main effects Cox regression model (HRm), and hazard ratios from final Cox regression model (HRf) for local recurrence

Variables	RRu	HRm	HRf
In Final Cox Model			
Non-colorectal-trained surgeon	2.79	2.92	2.49
< 21 resections by surgeon	1.62	1.84	1.80
Rectal perforation or tumour spill	2.01	2.46	2.86
Vascular or lymphatic invasion	1.68	1.99	1.69
Adjuvant therapy^			
preop	0.55	0.49	0.33
postop	1.30	1.34	0.79
Stage **			
2	2.14	2.72	2.74
3	3.46	4.66	4.62
Not in final Cox model			
Age***			
40-59	1.17	0.98	-
60-79	1.32	1.14	-
≥80	1.69	1.39	-
Male gender	0.91	0.92	-
Obstruction	1.67	1.75	-
Fixation	1.22	1.31	-
Margin < 2 cm	1.27	1.41	-
Abdominoperineal resection ***	1.08	1.04	-
Grade****			
2	1.54	1.60	-
3	2.09	2.80	-

^: comparison group is no adjuvant therapy

*: comparison group is stage = 1

**: comparison group is age < 40 years

***: comparison group is low anterior resection

****: comparison group is grade = 1

Table 6.5 Logistic regression model using perioperative mortality as the outcome (n=683)

	B	SE(B)	OR	95% CI	p value
Constant	-5.32	0.71			<0.001
Goldman Class *					0.001 [P]
2	1.81	0.82	6.13	1.23-30.67	0.03
3	3.02	0.83	20.45	1.39-103.90	<0.001

B: coefficient; SE: standard error of coefficient

OR: odds ratio; CI: confidence bounds for odds ratio

*: Comparison group is Goldman Class = 1

[P]: overall p-value

Table 6.6 Logistic regression model using ≥ 1 generic complication(s) as the outcome (n = 669)

	B	SE(B)	OR	95% CI	p value
Perioperative transfusion	0.91	0.21	2.48	1.65-3.75	<0.001
Non-colorectal-trained surgeon	0.67	0.29	1.95	1.10-3.45	0.02
Age *					0.05[P]
40-59	1.66	1.05	5.25	0.66-40.85	0.12
60-79	1.85	1.05	6.37	0.81-49.90	0.08
≥ 80	2.17	1.07	8.74	1.10-68.03	0.04
Constant	-4.03	1.09			<0.001

B: coefficient; SE: standard error of coefficient

OR: odds ratio; CI: confidence bounds for odds ratio

*: comparison group is age <40 years

[P]: overall p-value

Table 6.7 Logistic regression models using LAR-specific complications as the outcome (N=332)

	B	SE(B)	OR	95% CI	p value
Outcome: ≥ 1 LAR-specific complication					
< 21 resections by surgeon	0.75	0.31	2.11	1.15-3.84	0.01
Constant	-2.04	0.23			<0.001
Outcome: anastomotic leak ^{N}					
Male gender	1.29	0.65	3.64	1.01-13.20	0.05
Stapled anastomosis	0.67	0.29	1.95	1.40-14.09	0.01
Constant	-4.88	0.74			<0.001
Outcome: anastomotic stricture					
< 21 resections by surgeon	1.02	0.35	2.78	1.40-5.53	0.004
Stapled anastomosis	1.12	0.40	3.05	1.39-6.68	0.005
Constant	-3.23	0.41			<0.001

B: coefficient; SE: standard error of coefficient

OR: odds ratio; CI: confidence bounds for odds ratio

^{N} : n = 376

Table 6.8 Logistic regression model using ≥ 1 APR-specific complication(s) as the outcome (n = 261)

	B	SE(B)	OR	95% CI	p value
< 21 resections by surgeon	1.05	0.28	2.86	1.67-4.9	<0.001
Primary perineal closure[Ψ]	-0.31	0.31	0.73	0.40-1.34	0.01 *
Inadvertent rectal perforation/tumour spill[Ψ]	2.57	0.81	13.00	2.68-63.25	0.003 *
Constant	-0.98	0.29			0.001
Interaction term	-2.17	0.90			0.02

B: coefficient; SE: standard error of coefficient

OR: odds ratio; CI: confidence bounds for odds ratio

*: p value from model **excluding** interaction term

[Ψ]: Significant interaction between perforation/spill and perineal closure - see Table 6.9 for odds ratios adjusted for interaction

Table 6.9 Odds ratios of the effects of inadvertent tumour spill/rectal perforation and primary perineal closure on the outcome of ≥ 1 APR-specific complication, with adjustment for interaction

Primary perineal closure	Tumour spill/rectal perforation	OR	95% C.I.
absent	absent	1	-
present	absent	0.73	0.40-1.34
absent	present	13.0	2.68-63.25
present	present	1.09	0.25-4.81

Table 6.10 Linear regression model using the natural logarithm of length of stay as the outcome (n = 683)

	B	T statistic	p value
Age*	0.16	3.9	0.001
Goldman Class**	0.12	2.8	0.005
APR	0.27	7.4	<0.001
Perioperative transfusion	0.18	4.9	<0.001
Year of operation***	-0.10	3.0	0.003

B: coefficient

*: older patients at higher risk

**: higher class at higher risk

***: earlier years at higher risk

Chapter 7

Discussion and Conclusions

The purpose of this study was to determine if surgeon-related factors, namely subspecialty training in colorectal surgery and frequency of rectal cancer resection, were independent prognostic factors for various outcome measures in rectal cancer. In so doing, the prognostic significance of other factors was determined.

The cohort consisted of all patients undergoing potentially curative LAR or APR for rectal cancer in Edmonton over the eight-year interval of January 1, 1983 to December 31, 1990. Multiple data sources were used which included hospital discharge charts, Cross Cancer Institute charts, surgeons' office charts, family physicians' office charts, Alberta and several other provincial cancer registry data. Demographic, preoperative, intraoperative, pathologic, and adjuvant therapy variables were collected. Outcomes examined included perioperative mortality, local recurrence, survival, and perioperative morbidity. All hypotheses were examined analytically by means of multivariate statistical techniques.

7.1 Cohort Characteristics

A total of 683 patients were included in the study. Age and gender in this cohort were similar to other studies, as was tumour stage, grade, type, and level distribution.[116,117,155] The proportion of patients undergoing APR (44%) in this study was higher than most recent literature which claims sphincter preserving procedures may be performed in up to 90% of rectal cancer patients[100,156] However, this cohort of patients preceded much of this literature.

Moreover, most studies with a high proportion of sphincter-preserving procedures originate from specialized centers, with a small number of surgeons, all with a particular interest in rectal cancer surgery. This study, however, did show that both colorectal-trained surgeons and those performing ≥ 21 resections were more likely to perform LAR and thus preserve the anal sphincter. Moreover, with colorectal-trained surgeons, this occurred despite the fact that they treated more low-level tumours.

It is difficult to explain the association between low-level tumours and colorectal-trained surgeons, especially as there were no referrals between the surgeons in this study. It is possible that gastroenterologists are more likely to refer the more difficult low rectal tumours to colorectal-trained surgeons, however, the data necessary to determine this was unavailable.

A small proportion of patients in this study (16%) was treated by colorectal-trained surgeons. There are two likely explanations for this finding:

1. Only 5 of the 53 surgeons involved were colorectal trained, with one of these colorectal-trained surgeons beginning practice only in the final year of the study (1990). The lack of availability of expertise (colorectal-training) thus may explain the fact that most operations were performed by non-colorectal-trained surgeons.

2. Although it was not possible to ascertain the referral source in all patients, there was not a single case identified in which a non-colorectal-trained surgeon referred a rectal cancer patient to a colorectal-trained surgeon for performance of the initial resection. This suggests that over the study period, non-colorectal-trained surgeons felt comfortable with the primary treatment of rectal cancer.

Owing to the large number of surgeons involved in this study, the number of resections performed by each surgeon, irrespective of colorectal training, was often quite small, with only 13 of 53 surgeons performing at least 21 resections over the study period. This variable simply indicates the experience of the surgeon with rectal cancer surgery, although it also may reflect a surgeon's interest in rectal cancer surgery. Other studies in rectal cancer have not reported the distribution of surgeon experience, thus making comparison impossible.

7.2 Local Recurrence

The overall local recurrence rate in this study (33.8%) falls within the broad range reported in the literature (2.6%-38%) [113 - 120,134,135] although it is certainly quite high compared with the more recent large series.[100,118,136,155] A possible explanation for the high local recurrence rate observed may lie in the study definition of local recurrence. All patients with CT scan evidence of local recurrence were presumed so even in the absence of histologic proof, as no effort to confirm the local recurrence was made in most of these patients. This was the case in 56 of 205 (27.3%) of all patients with local recurrence. Many studies limit local recurrence to histological proven cases. Thus, the possibility of false positive local recurrence exists. This is likely minimal, however, because 53 of these 56 patients died of rectal cancer, indicating recurrence elsewhere, and radiographic progression of local recurrence was seen in 81% of cases. Furthermore, all outcome analyses of local recurrence were repeated requiring histologic proof of local recurrence which resulted in minimal changes in the findings. The observed local recurrence rate therefore appears valid.

Numerous factors identified on univariate analysis were found to be statistically associated with local recurrence. However, on multivariate analysis, only operation performed by a non-colorectal-trained surgeon, operation performed by a surgeon performing <21 resections, advanced stage, vascular or lymphatic invasion, rectal perforation or tumour spill, and the absence of adjuvant therapy were found to be independent prognostic factors for local recurrence (Table 6.2). The confounding effects of many of the variables identified on univariate analysis reinforces the limitations of univariate analysis to examine prognostic factors in rectal cancer.

Local recurrence was significantly lower in patients of colorectal-trained surgeons than in those of non-colorectal-trained surgeons (Hazard ratio (HR) = 2.5). Operative technique almost certainly contributed to this finding, although firm evidence in this regard is lacking. The retrospective review of the operative reports made assessment of the presence or degree of mesorectal excision impossible to determine.

Similarly, local recurrence was significantly lower in patients of surgeons performing ≥ 21 resections than in those of surgeons performing <21 resections. The decision to dichotomize this variable about its median (21 resections) was made a priori to provide a clinically meaningful variable and to preserve statistical power. This finding of increased local recurrence risk with decreasing surgeon experience is supported by the dose-response gradient demonstrated in Figure 7.1 where local recurrence curves are demonstrated for surgeons of the lower quartile, middle quartiles, and upper quartile in terms of number of resections performed over the study period. Furthermore, when substituting this three-level categorical variable for the dichotomous frequency of resection variable from Table 6.2, a similar trend of increased relative risk of local recurrence among surgeons performing in the lower quartile number of resections (RR=1.4) and among those performing in the middle quartiles (RR=1.1). However, this does not attain statistical significance, largely as a result of loss of power.

Stage, vascular/lymphatic invasion, and inadvertent rectal perforation or tumour spill are well accepted prognostic factors for local recurrence.[85,86,91,100,101,103] The use of adjuvant therapy was independently associated with lower local recurrence, with the most marked benefit seen when the adjuvant therapy was given preoperatively. This finding existed despite the heterogeneous radiotherapy doses and varying chemotherapeutic regimes used over the study period. Undoubtedly, this study design is suboptimal in determining the role of adjuvant therapy in the treatment of rectal cancer. However, control of its potential confounding effects was essential to the testing of our hypotheses. Although some studies in which rectal cancer prognostic factors have been examined retrospectively have suggested a benefit to adjuvant therapy, others have not.[91,100,103,117,118] Most recent clinical trials seem to indicate a benefit to preoperative adjuvant therapy, and it is such trials upon which adjuvant therapy decisions should be based. [41,68,69,155]

7.3 Survival

The overall disease-specific survival rate was 46.3%, with a 5-year disease-specific actuarial survival of 59.0%. Five-year actuarial rates are presented in most other series, ranging from 49% - 68%.[116,157 - 161] Thus, the survival experience seen in this series appears within the range of what is expected from the literature.

On multivariate analysis, the presence of a non-colorectal-trained surgeon, the presence of a surgeon performing <21 resections, advanced stage, vascular or lymphatic invasion, rectal perforation or tumour spill, advanced stage, advanced grade, and older age were found to be independent prognostic factors for disease specific survival (Table 6.1). As was noted in the analysis of local recurrence, the confounding effects of many of the variables identified on univariate analysis reinforces the limitations of univariate analysis to examine prognostic factors in rectal cancer.

The biologic explanation for improved disease-specific survival in both colorectal-trained surgeons and surgeons performing ≥ 21 resections is likely a direct result of the decreased local recurrence rate among these surgeons. The vast majority of rectal cancer patients who develop local recurrence will die of their disease,[162] a finding confirmed in this study where 92.7% of those patients with local recurrence died of rectal cancer. Most local recurrences in rectal cancer occur in the absence of metastatic disease elsewhere.[116,163,164] Rectal cancer deaths that occur in patients with local recurrence are the result of local complications of tumour growth as well as the development of systemic metastasis from a high local tumour burden.

As was shown for local recurrence, a dose-response gradient for number of resections performed by the surgeon is shown in Figure 7.2 where disease-specific survival curves are demonstrated for surgeons of the lower quartile, middle quartiles, and upper quartile in terms of number of resections performed by the surgeon over the study period. As noted for local recurrence, when substituting this three-level categorical variable for the dichotomous frequency of resection variable from Table 6.1, a similar trend of increased risk of disease-specific mortality among surgeons performing in the lower quartile number of resections (RR=1.3) and among those performing in the middle quartiles (RR=1.2). Again, this did not attain statistical significance, largely as a result of loss of power.

Stage, grade, vascular/lymphatic invasion, and inadvertent rectal perforation or tumour spill are accepted predictors for survival.[85,86,91,100,101,103] Although definitely a predictor for overall survival, the prognostic value of age for disease-specific survival is less defined. Some have suggested patients <40 years of age have a worse prognosis.[165] However, this appears to be the result of more advanced stage and higher grade disease in these patients.[166,167] This study found a lower disease-specific survival in all age groups compared to patients <40. However, the risk of disease-specific mortality in patients 60-79 years of age (HR = 1.91) was greater than the risk in patients ≥ 80 years (HR = 1.67). Regardless, a clinical or biological explanation for the apparent improved disease-specific survival in patients < 40 years, after controlling for potential confounding factors, is lacking. A plausible, but as yet unproved explanation may lie in the loss of "cancer-specific immunity" that accompanies aging.[168]

The outcome of survival may be interpreted in several fashions. Several studies report survival without specifying whether their measure related to disease-specific or all cause mortality. Disease-specific survival was presented in Chapters 6 as the measure of survival. Similar analyses also were performed on the outcomes of event-free survival (where any cancer recurrence was considered an event) and overall survival (where death of any cause was considered an event). Independent prognostic factors from these models were the same as the factors identified for disease-specific survival. Moreover, there were only small differences in risk estimations for each factor. Thus, the prognostic factors identified in Table 6.1 appear to be valid regardless of the specific type of survival examined.

7.4 Perioperative Mortality

Published perioperative mortality rates vary from 0.8% - 9.6%, with the majority of studies reporting rates of 2%-4%.[117,157,158,169,170] The perioperative mortality rate in this study (2.0%) compared favourably. This is despite a somewhat more liberal definition of perioperative mortality to include not only all deaths within 30 days of surgery, but also to include all deaths during the same hospitalization, regardless of interval from surgery. Because preoperative Goldman Class, a validated measure of risk of perioperative cardiac mortality, was found to be the only independent risk factor for perioperative mortality, the relatively low perioperative mortality may be explained by differences in baseline health status. Unfortunately, none of the rectal cancer studies with stated perioperative mortality rates documented the breakdown of Goldman Class among their patients.

In reference to a secondary objective of this study, neither surgical subspecialty training in colorectal surgery nor frequency of rectal cancer resection by the surgeon were significant independent risk factors for perioperative mortality. However, the power of this analysis was limited as a result of the small number of perioperative deaths (14) and thus the confidence to conclude that neither surgical colorectal training nor frequency of resection by the surgeon affect perioperative mortality risk was limited. This limited power was particularly important in interpreting the trend toward higher perioperative mortality in patients treated by non-colorectal-trained surgeons compared with those treated by colorectal-trained surgeons (2.3% vs. 0.9%).

7.5 Postoperative Morbidity

Several measures of postoperative morbidity were used in this study. Generic complications were believed to represent the typical postoperative complications following any major abdominal operation. The pathophysiology explaining the observed reduction in patients with ≥ 1 generic complication among colorectal-trained surgeons is likely multifactorial. Certainly, technical factors likely play a role, especially for complications such as abdominal wound dehiscence and intraabdominal sepsis, although identification of those specific technical factors was impossible in this study. Quality of postoperative care also may play a role, although again this is difficult to quantify.

In contrast to generic complications, surgeon experience, rather than training, appeared to be most important in the development of specific procedure-related complications. Both LAR-specific and APR-specific complications are the direct result of technical factors, as is evidenced by the other independent prognostic factors identified (male gender, stapled anastomosis, primary perineal closure, inadvertent rectal perforation or tumour spill). This study suggests that the avoidance of such complications is directly related to the experience of the surgeon, as measured by the number of resections performed by the surgeon. It is possible that improvements in operative technique, so as to reduce the likelihood of these procedure-specific complications, are made by the surgeon as he/she gains experience.

Length of stay in hospital for many procedures has decreased markedly in North America.[171] Thus, it was critical to control for year of operation in examining length of stay as a measure of postoperative morbidity. No surgeon-related factors were found to be independent predictors of length of stay. In fact, many of the identified predictors, including age, Goldman Class, and year of operation, could be considered unalterable. As found in this study, it has been reported that patients undergoing APR have longer lengths of stay than those undergoing LAR.[172] As both colorectal-trained surgeons and surgeons performing ≥ 21 resections appeared to preferentially select LAR for mid- and low-level tumours, their choice and ability to perform this operative procedure indirectly may have reduced length of stay.

Hospital stay following a given surgical procedure may be influenced by many variables. Some of these variables are obvious and easy to measure (comorbidity, age)[173] while others are more difficult to measure (operative technique, physician attitudes and efficiency).[174] Moreover, factors may vary between countries based on differing health care systems thus limiting the generalizability of studies. In a recent U.S. study examining length of stay following colorectal cancer resections in a multivariate analysis, Tartter (1996)[172] established a model containing very similar variables to those found in this study.

7.6 Summary of Conclusions

Both surgical colorectal training and a greater frequency of rectal cancer resections by the surgeon improve outcome in rectal cancer in terms of local recurrence and ultimate survival. An aggressive approach by these surgeons to perform LAR for low- and mid-level rectal tumours, thus preserving the anal sphincter, does not increase recurrence.

Similarly, both surgical colorectal training and a higher frequency of resections by the surgeon are associated with a reduction in specific selected postoperative complications. Length of stay in hospital and perioperative mortality appear to be largely related to patient factors, although a trend (not statistically significant) towards reduced perioperative mortality was noted in patients of colorectal-trained surgeons.

7.7 Agreement of the Major Findings with the Literature

Consistency of with results reported in the literature adds to the validity of a study's findings. Improved outcome with higher frequency surgeons found in this study of rectal cancer analogously has been shown with respect to long-term survival in breast cancer[131] and with respect to postoperative morbidity in periampulary cancer.[133]

Specifically in rectal cancer, there have been no previous studies examining the prognostic effect of specific surgeon-related factors in a valid fashion. The variations in survival and local recurrence rates between individual surgeons shown in previous studies[112,144,145] certainly may be explained by the surgeon-related factors (training and/or experience) identified in this study.

7.8 Limitations

In accepting the validity of the results of this study, one may argue that they apply only to the setting involving the specific surgeons participating in the study. However, because this study examined the impact of surgeon related-factors, as opposed to individual surgeons, on outcome, the generalizability could be extended to centres where similar surgeon-related factors are present. To the author's knowledge, a similar structure of surgeon-related factors exists in many locations in North America. The generalizeability to centres where such similar surgeon-related factors are not present would be questionable. For example, the prognostic importance of the number of rectal cancer resections performed by the surgeons found in this study may not apply to a centre where all rectal cancer surgery was performed by colorectal-trained surgeons.

This patient cohort represents resectable rectal cancer from five urban hospitals. Thus, the generalizeability of the results of this study to rural areas with "rural" surgeons may be questionable. The "rural" general surgeon likely performs a wider range of procedures than the "urban" general surgeon, although any one procedure may be performed more infrequently by the "rural" surgeon. As "rural" surgeons were not included in this study, the observed (worsened) outcome observed among surgeons performing rectal cancer resections less frequently may not be representative of the "rural" surgeons' results. Further research in this area may be warranted.

The validity of retrospective cohort studies may be limited by the presence of unknown or unmeasureable confounding factors. Although an attempt was made to identify and analyze all known and potential prognostic factors, it is possible that an unknown or unmeasurable prognostic factor existed. However, to affect this study's validity, such a factor would also need to confound or modify the effect of the surgeon-related variable in question.

There was no evidence of any referral bias, because all hospitals in the city were included in this study. However, the effect of patients who may have been declined surgery in the study region and referred out and vice versa could not be directly assessed in this retrospective study. Indirect evidence suggests that this did not occur disproportionately between the surgeon-related groups as their demographic and preoperative variables characteristics were similar.

Perhaps the most important limitation of this study is its inability to conclusively explain, on a biologic basis, the observed improved outcome among patients of colorectal-trained surgeons and those of surgeons performing a greater frequency of rectal cancer surgery. This is not simply a question of "good" and "not so good" surgeons, for if it were, one would conclude that 39 of the 52 (75%) surgeons fell into the "not so good" group. It is more likely that specific operative techniques in rectal cancer surgery are responsible for the improvement seen in specific groups of surgeons. However, the ability to retrospectively identify specific operative factors is difficult. Thus, the identification of these factors would best be done in a comprehensive prospective fashion.

7.9 Recommendations

Prior to any specific recommendations, a brief discussion of potential surgeon resources is required. This study shows that there are approximately 80 - 100 potentially curative rectal cancer resections performed per year in Edmonton. Divided among four or five surgeons, this would amount to 20-25 resections per year by each surgeon, or approximately one resection every two weeks. This is certainly a manageable number of procedures and would not result in any monopolization of institution or individual surgeon's operating room resources.

If these 80 - 100 potentially curative resections are divided among all general surgeons in the city, 2-3 resections per year would be performed by each surgeon, assuming a relatively equal distribution of cases. In terms of direct physician reimbursement, this represents $1,679.96 - $2,534.19 per year.[175] However, loss of these cases would not necessarily result in loss of this income as the surgeon's allotted operative time could be filled with other procedures.

The following recommendations are made based on the results of this study. They are to apply to centres where a similar distribution of surgeon-related factors as was found in this study exist.

1. Because outcome is improved among surgeons with colorectal training and those performing a higher number of resections, the surgical treatment of rectal cancer should be the exclusive domain of surgeons with such training and/or experience.

2. An aggressive approach should be maintained by trained, experienced surgeons to perform LAR for mid- and low-level rectal tumours where possible.

3. Future studies examining outcome in rectal cancer should consider the effect of surgeon-related factors. Specifically, randomization stratified by surgeon-related factors may be an appropriate technique in rectal cancer clinical trials.

4. Because technical factors likely play a role in rectal cancer outcome, further prospective research is required to elucidate these factors, both as they relate to cancer-specific outcomes such as local recurrence and survival, and as they relate to postoperative morbidity.

" The concept that surgeons might vary in their ability to obtain good short and long term results is usually hotly debated and then rejected, as are many perturbing ideas in professions steeped in dogma and ritual"

L.P. Fielding (1988)[139]

Just as it is incumbent upon the surgeon to use evidence to critically assess patient management strategies, a similar approach should be adopted in determining who should provide such management.

Figure 7.1 Kaplan Meier curves for local recurrence by number of rectal cancer resections performed by the surgeon (< 25th, 25th-75th, >75th percentile)

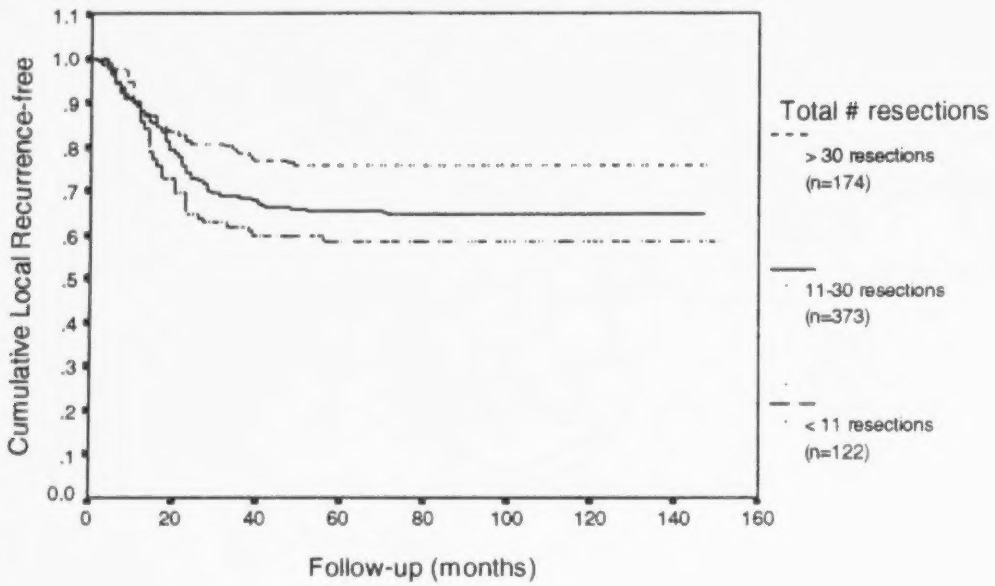
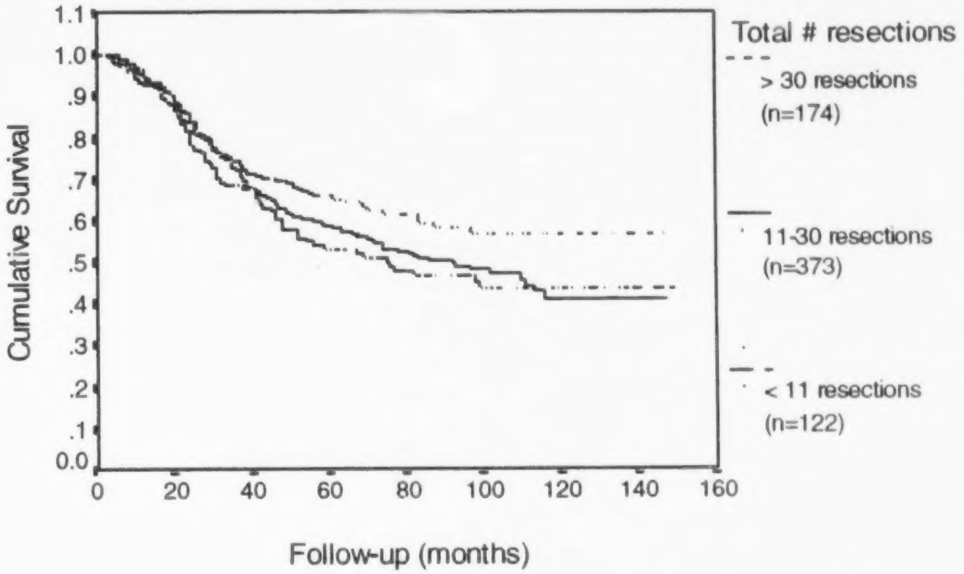


Figure 7.2 Kaplan Meier curves for disease-specific survival by number of rectal cancer resections performed by the surgeon (< 25th, 25th-75th, >75th percentile)



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Appendices

Appendix 1: TNM Staging System

T - tumor

T0 - No evidence primary tumor

Tis - Intraepithelial or invasion of the lamina propria

T1 - Tumor invades submucosa

T2 - Tumor invades the muscularis propria

T3 - Tumor through muscularis propria into subserosa , non peritonealized pericolic, or perirectal tissues

T4 - Tumor invades other organs and/or visceral peritoneum

N - lymph nodes

NX - Regional lymph nodes cannot be assessed

N0 - No regional lymph nodes metastasis

N1 - Metastasis in 1-3 regional nodes

N2 - Metastasis in 4 or more nodes.

N3 - Metastasis in any lymph node along the course of a named vascular trunk

M - metastasis

MX - Presence of distant metastasis cannot be assessed

M0 - No distant metastasis

M1 - Distant metastasis

Stage

	Tumor	Lymph Nodes	Metastasis
Stage 0	Tis	N0	M0
Stage 1	T1 or T2	N0	M0
Stage 2	T3 or T4	N0	M0
Stage 3	Any T	N1-N3	M0
Stage 4	Any T	Any N	M1

Appendix 2: Letter to Primary Care Physician

October 20, 1995

Dr.Geoff Porter
11429 University Ave.
Edmonton, Alberta
T6G 1Y9

Primary Care Physician
Address

Dear Primary Care Physician:

I am writing in regards to research currently being jointly conducted by the departments of Surgery and Public Health Sciences at the University of Alberta. This project is entitled "Surgeon-related Variability and Outcome in Rectal Cancer" and will attempt to examine the impact of colorectal training and frequency of rectal cancer surgery on outcome in rectal cancer.

In gathering data for the study, your assistance would be appreciated in providing any follow-up information regarding **<Patient>**, a patient believed to be (or have been) in your practice. To this point, sufficient follow-up information regarding this patient has not been obtained from the hospital charts, surgeons' office charts, or Cross Cancer Institute. Thus, we are asking you to complete the enclosed Reply Form and return it in the enclosed self-addressed envelope.

I have included with this letter an outline of the study protocol which briefly describes the objectives and methods of the study. Should you wish more detailed information, a formal research proposal is available upon request. The study will maintain confidentiality and privacy of all patients and all physicians involved. Specifically, individual physicians will at no point be identified and no analysis comparing individual surgeons will be performed. This research has been approved by the Ethics Board of the University of Alberta as well as the Cross Cancer Institute.

Your cooperation is vital to this study and greatly appreciated. If you have any questions or concerns, please feel free to contact me at any time by letter or through the University of Alberta switchboard.

Thank you very much for your attention in this matter and I look forward to hearing from you.

Yours sincerely,

Geoff Porter M.D.

Appendix 3: Reply form from Primary Care Physician

Patient: **<patient's name>** Physician: **< physician's name>**

1. Date of last patient contact: ___________

2. Was patient living? Yes __ (go to 5)
   No __ (go to 3)

3. If deceased, date of death (month/year): _______

4. If deceased, did patient die of rectal cancer? Yes __
   No __

5. If patient was living, what was the status of their rectal cancer?
   No residual disease __

   Alive with metastasis __

6. If patient alive with metastasis, please specify:
   a. site(e.g. liver, pelvis, lung): ____________________

   b. date metastasis detected (month/year): ___________

7. To your knowledge, did the patient suffer any complications of their original operation for rectal cancer?
   Yes __
   No __

   If yes, please specify: ____
____

Comments:____
____
____

Thank you for your time and assistance in this research.

Appendix 4: Outline of Study Protocol

Title: Surgeon-related Variability and Outcome in Rectal Cancer.

Investigators: G Porter, C Soskolne, W Yakimets, S Newman, K Bay.

Research questions (objectives):

1. To determine the prevalence of rectal cancer operations being performed by colorectal - trained surgeons.
2. To determine if presence of subspecialty training in colorectal surgery or interest in rectal cancer surgery is a risk factor for perioperative mortality or morbidity, local recurrence or survival.

Significance (background):

1. Rectal cancer is relatively common malignancy with a 5-year survival of 47%.
2. There is both direct and indirect evidence in the literature that there is a surgeon-related variability in outcome from rectal cancer.
3. Knowledge of any outcome advantage within a subgroup of surgeons would provide some justification for specialization of care to specific institutions and/or specific surgeons.

Design: A retrospective cohort study with descriptive and analytic components.

Subjects

Selection criteria: Rectal cancer patients undergoing resection at one of five Edmonton hospitals.

Sampling design: All patients over a seven year period (1983-1990).

Variables

Predictor variables: Presence of colorectal-trained surgeon, interest in rectal cancer surgery (as deemed from frequency of resections performed).

Potential confounding variables: Age, sex, inadvertent perforation, level of tumor, operation performed, blood transfusion, stage, grade, adjuvant therapy.

Outcome variables: Postoperative morbidity and mortality, local recurrence, event-free survival, overall survival.

Statistical issues:

Hypothesis and analytic approach:

1. The prevalence objective will be analyzed as the proportion who have their operation performed by a colorectal-trained surgeon, with 95% confidence intervals in various stage, level and type of operation groups.
2. The analytic objective has the hypothesis that patients of colorectal-trained surgeons will have better outcomes than patients of non colorectal-trained surgeons. A second analytic objective has the hypothesis that patients of surgeons with higher frequency of rectal cancer resections will have better outcomes than patients of surgeons with lower frequency of resections. Predictors of the various outcome variables will be analyzed by various regression techniques.

Appendix 5: Letter to Provincial Cancer Registry/Health Department

January 8, 1996

Dr.Geoff Porter
11429 University Ave.
Edmonton, Alberta
T6G 1Y9

Provincial Health Department
<Address>

Dear <suggested contact as per Alberta Health>:

I am writing in regards to research currently being conducted by the Departments of Surgery and Public Health Sciences at the University of Alberta. This project is entitled "Surgeon-related Variability and Outcome in Rectal Cancer" and will attempt to examine the impact of colorectal training and frequency of rectal cancer surgery on outcome in rectal cancer. I am a General Surgery Resident currently completing an MSc. in Public Health. My supervisor is Dr. Colin Soskolne.

This study involves the follow-up of all patients undergoing surgery for rectal cancer in Edmonton over the period 1983-1990, approximately 700 patients. We have insufficient follow-up information regarding 35 of these patients through the Alberta Cancer Registry and feel that this may be a result of their relocation to a different province. Thus, we are contacting several provincial health departments in an attempt to ascertain the vital status of these patients. The following is a list of patient names and birthdates.

< list deleted for confidentiality>

Thus, we are requesting vital status information (alive, deceased), date of death (if applicable), and cause of death (colorectal cancer/other) of any of the above patients. A reply form and self-addressed envelope is enclosed for this purpose.

I have included with this letter an outline of the study protocol which briefly describes the objectives and methods of the study. Should you wish more detailed information, a formal research proposal is available upon request. The study will maintain confidentiality and privacy of all patients and all physicians involved. Specifically, individual physicians will at no point be identified and no analysis comparing individual surgeons will be performed. This research has been approved by the Ethics Board of the University of Alberta as well as the Cross Cancer Institute.

Your cooperation is vital to this study and greatly appreciated. If you have any questions or concerns, please feel free to contact me at any time by letter or through the University of Alberta switchboard (403 492-8899).

Thank you very much for your attention in this matter and I look forward to your reply.

Yours sincerely,

Geoff Porter M.D.

Reply Form

Province: <province name>

Patient Name	**DOB**	**Vital Status (Alive/Deceased)**	**Date of death ***	**Death from colorectal cancer (Yes/No)***

* - if applicable

Appendix 6: Precoded Data Form

Code I.D.:____________

Name(last,first,init.):______________________ I.D.(Hosp, #):____________

Sex: M(1)__ F(0)__ Cross Cancer I.D. #:____________

D.O.B.(D/M/Y):________ Age (at Dx): ______

Date of Dx (M/Y):__________ Hospital (UAH=1, RAH=2,GNH=3, MIS=4): _____

Primary Care Physician: _________________________ Tel. #: ____________

Comments:____

____

____

Preoperatively

Fixed clinically (Y=1, N=0, not stated=9): _____ Preop CEA: ____

Distance from anal verge:____cm Goldman (#, class):_____

Operatively

Surgeon:_______________ Colorectal trained(Y=1, N=0): _______

Date of Surgery(D/M/Y): _________

Procedure (LAR=1, APR=0): _____

- If APR, two-teamed (Y=1, N=0): ______
- If APR, Perineum closed (Y=1, N=0): _____
- If LAR, stapled(1) or hand-sewn(0):_____
- If LAR, diverting ostomy (1) or none(0): ______

N/A = 8

Inadvertent perforation of rectum (Y=1,N=0): _____

Intaoperative tumour spillage (Y=1, N=0):_____ Blood Transfusion(Y=1,N=0):_____

If yes, # units: _____

Operative time (minutes): ________

Operative Mortality

Perioperative death (Y=1, N=0): ______

Cause: ____

Operative Morbidity

Pneumonia (Y=1, N=0): ______

Wound infection - Abdominal (Y=1, N=0):____
Perineal (Y=1, N=0, N/A=8): _____ (APR only)

Perineal Sinus (Y=1, N=0, N/A=8): ____ (APR only)
If yes, duration of drainage(months, N/A=99): ____

Colostomy complications (Y=1, N=0, N/A=8): _______ (APR only)

Anast. leak (Y=1,N=0,N/A=8):___ (LAR only) If yes, reop.? (Y=1,N=0,N/A=8):___

Anast stricture (Y=1,N=0,N/A=8): ___ (LAR only) If yes, reop. (Y=1,N=0,N/A=8):___

Length of hospital stay (days):______

Comments: ____

____

____

Pathology

T (0-4): ____ N(0-3):____ M(0-1):____ Stage (1-4):_______

Grade (1-4): _____ Number lymph nodes: ________

Margins: Proximal (cm): ____
Distal (cm): ______
Radial negative (Y=1, N=0,unknown=9): ______

Size(cm): _______ Distance from anal verge(cm):______

Type (adenoCA NOS=1, +mucin=2,signet ring=3, other=4): ____

Angio/lymph/neural invasion (Y=1, N=0):_______

Adjuvant Therapy

Adjuvant therapy (1-5): _______

1= preop RTx
2= preop chemo + RTx
3= postop RTx
4= postop chemo + RTx
5= No adjuvant therapy

If RTx, dose (cGy):_______________ If chemo,agent(s):____________

____

Reason for adjuvant Rx: ____

Follow-up

Local recurrence (Y=1, N=0, unknown=8,lost to F/U=9): _______

If yes, time to LR (months): ______

If yes, location: _____ anastomotic (LAR only)=(1)
pelvic=(2)
perineal (APR only)=(3)

5-year event-free survival (same as LR): _____ If no, time to event (months):_____

5-year survival (same as LR): ______ If no, time to death (months):__________

If unknown (8), cause of death:____

Follow-up (months):_________

Comments:____

____

____

Appendix 7: List of variables on the working file

Name			Position
ID	identification		1
SEX	gender		2
	0	female	
	1	male	
AGE	age at diagnosis (yrs)		3
YR	year of operation		4
	83	1983	
	84	1984	
	85	1985	
	86	1986	
	87	1987	
	88	1988	
	89	1989	
	90	1990	
WGT	weight (kg)		5
HOS	hospital of operation		6
	1	University	
	2	Royal Alexandra	
	3	Grey Nuns'	
	4	Misericordia	
	5	Charles Camsell	
FIX	preoperative tumour fixation		7
	0	no	
	1	yes	
OBS	preoperative complete obstruction		8
	0	no	
	1	yes	
CEA	preoperative CEA (mg/dl)		9

LEV preop level from dentate line (cm) 10

GO# goldman index # 11

GOC goldman class 12

1 I
2 II
3 III

SUR surgeon 13

Coded 1-53

COL colorectal-trained surgeon 14

0 no
1 yes

ORP operative procedure performed 15

Missing Values: 2 thru 9

Value Label

0 Abdominoperineal resection
1 Anterior resection

TTA two-teamed approach 16

Value Label

0 no
1 yes
8 not applicable

SU2 2nd surgeon if 2-teamed (see sur) 17

PER if APR, primary perineal closure 18

0 no
1 yes
8 not applicable

STP	if LAR, anast sewn or stapled	19
	0 handsewn 1 stapled 8 not applicable	
OST	if LAR, diverting ostomy used	20
	0 no 1 yes 8 not applicable	
IPR	inadvertent perforation of rectum	21
	0 no 1 yes	
ITS	intraoperative tumour spill	22
	0 no 1 yes	
MIN	operative time (minutes)	23
ENB	enbloc resection	24
	0 no 1 vagina 2 ovary(ies) 3 TAHBSO 4 bladder 5 small bowel 6 other 7 combination of above	
EBL	estimated blood loss (ml)	25
TRA	perioperatve transfusion	26
	0 no 1 yes	

NTR number units transfused 27

MOR perioperative mortality 28

0 no
1 yes

PNE perioperative pneumonia 29

0 no
1 yes

AWO abdominal wound infection 30

0 no
1 yes

PWO perineal wound infection 31

0 no
1 yes
8 not applicable

PSI perineal sinus 32

0 no
1 yes
8 not applicable
9 unknown

PSD duration of sinus drainage (months) 33

99 not applicable

CCO colostomy complication req. OR 34

0 no
1 yes
8 not applicable

ANL anastomotic leak 35
0 no
1 yes
8 not applicable

LRE if leak, reoperation 36

0 no
1 yes
8 not applicable

ANS anastomotic stricture 37

0 no
1 yes
8 not applicable

SRX treatment for stricture 38

0 dilatation
1 operation
8 not applicable

DEH wound dehiscence 39

0 no
1 yes

ASE postop abdominal sepsis 40

Value Label

0 no
1 yes

UTI postoperative uti 41

0 no
1 yes

URE postop urinary retention 42

0 no
1 yes

SBO small bowel obstruction/ileus 43
0 no
1 yes, no OR
2 yes, required laparotomy

LOS	length of hospital stay (days)	44
T	depth of tumor (TNM)	45
N	lymph node stage (TNM)	46
STA	stage (TNM)	47
	1 - 1 2 - 2 3 - 3 4 - syncronous liver resection for cure	
GRA	grade	48
	1 well differentiated 2 moderately differentiated 3 poorly differentiated/undifferentiated	
NLN	number lymph nodes	49
PRO	proximal margin (nearest cm)	50
DST	distal margin (nearest 0.5 cm)	51
RAD	radial margin negative	52
	1 yes 9 unknown	
SIZ	tumor size	53
DAV	distance from anal verge (path,cm)	54

99 not applicable

TYP	histological type		55
	1	adenocarcinoma	
	2	mucinous	
	3	signet ring	
	4	other	
INV	angio/lymph/vascular invasion		56
	0	no	
	1	yes	
ADJ	adjuvant therapy		57
	0	none	
	1	preop radiotherapy	
	2	preop chemo + radiotherapy	
	3	postop radiotherapy	
	4	postop chemo + radiotherapy	
RTD	radiotherapy dose (cGy)		58
	0	not applicable	
CHE	chemotherapeutic agent(s)		59
	0	not applicable	
	1	5 F-U only	
	2	5 F-U and levamisole	
	3	5 F-U and follinic acid	
	4	other	
LR	local recurrence		60
	0	no	
	1	yes	
LRF	local recurrence F/U (months)		61
LRS	initial local recurrence site		62
	1	anastomosis only	
	2	pelvis only	
	3	perineum only	
	4	anastomosis and pelvis	
	8	not applicable (no local recurrence]	

LRD method of Dx of local recurrence 63

0 tissue Dx
1 radiological Dx
8 not applicable [no local recurrence]

EFS event free survival 64

0 no
1 yes

EFF event free survival F/U (months) 65

WHE site of first recurrence 66

0 no recurrence
1 local
2 metastatic
3 local and metastatic

DSS disease specific survival 67

0 no
1 yes

DSF disease specific survival F/U (months) 68
Print Format: F3
Write Format: F3

OVS overall survival 69

0 no
1 yes

OVF overall survival F/U (months) 70

DOC non rectal cancer death 71

0 no
1 yes

OTH	cause of non rectal cancer death	72

0	not applicable
1	cardiovascular
2	cerebrovascular
3	respiratory
4	other cancer
5	other cause
6	undefined

COM	complete follow-up	73

0	no
1	yes

YRF	year of last follow-up	74

0	complete
84	1984
85	1985
86	1986
87	1987
88	1988
89	1989
90	1990
91	1991
92	1992
93	1993
94	1994
95	1995

COMMENTS	75

Appendix 8: Goldman Index and Classification

	Points
S3 gallop on physical exam	11
Increased jugular venous distension on physical exam	11
Myocardial infarction in past 6 months	10
> 5 premature ventricular contactions/min.	7
ECG rhysth other than sinus	7
Any premature atrial contractions on ECG	7
Age over 70 years	5
Emergency operation	4
Intrathoracic, intraperitoneal, or aortic surgery	3
Evidence significant aortic stenosis	3
At least one of:	3
$K^+ < 3.0$ meq/L	
BUN > 12.0 meq/L	
Creatinine > 120 meq/L	
$HCO^{3} < 20$ meq/L	
$Po_2 < 60$ mm Hg or $Pco_2 > 50$ mm Hg	
Chronically bedridden	

0 - 5 points ➡ Goldman Class 1

6 - 12 points ➡ Goldman Class 2

13 - 25 points ➡ Goldman Class 3

> 26 points ➡ Goldman Class 4

Appendix 9: Ethics Approval

University of Alberta
Edmonton
Canada T6G 2R7

Faculty of Medicine
2J2.00 WC Mackenzie Health Sciences Centre
Telephone: (403) 492-6621
Fax: (403) 492-7303
E-mail: _____@dean.med.ualberta.ca

RESEARCH ETHICS BOARD

ETHICS APPROVAL FORM

Date: June 1995

Name(s) of Principal Investigator(s): Dr. W. Yakimets

Department: Surgery

Title: Surgeon-related variability and outcome in rectal cancer

The Research Ethics Board (REB) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information materials and consent form.

Specific Comments:

Signed - Chairman of Research Ethics Board

for the Faculty of Medicine
University of Alberta

This approval is valid for one year.

Our File #1835

Appendix 10: Letter to surgeon requesting permission to review office charts

Dr. Geoff Porter
Dvorkin Lounge, 2G1
Walter MacKenzie HSC
Edmonton, Alberta

July 1, 1995

Dear Surgeon,

For my research year in general surgery, I am doing a Masters' degree in Public Health Sciences. My thesis is titled "Surgeon-related variability and outcome in rectal cancer" and will attempt to examine the impact of colorectal training and frequency of rectal cancer surgery on outcome in rectal cancer.

I will be reviewing all patients' charts who underwent abdominoperineal or anterior resection from 1983 to 1990. These patients will be identified via hospital discharge diagnosis codes and followed through charts from the Cross Cancer Institute, family doctors' offices, and surgeons' offices. The purpose of this letter is to ask your permission to review your office charts of patients in this study. The study will maintain confidentiality and privacy of all patients and all physicians involved. Specifically, individual surgeons will at no point be identified and no analysis comparing individual surgeons will be performed. The only analysis will be of colorectal training and frequency of rectal cancer surgery.

I have included with this letter an outline of my study protocol which briefly describes the objectives and methods of the study. Should you wish more detailed information, a formal research proposal is available upon request. In addition, you will find a return stamped envelope and reply letter for you to fill in and return. If you have any questions or concerns, please feel free to contact me at any time by letter or through the University of Alberta switchboard.

Thank you very much for your attention in this matter and I look forward to hearing from you.

Sincerely,

Geoff Porter

Reply

Please check one or more of the following options and feel free to include any comments.

__ I give permission for my office charts to be used as a data source for the study.

__ I do not give permission for my office charts to be used as a data source for the study.

__ I request more information regarding the study

Comments:____

____

____

____

____

____

Surgeon